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Behavior of Infants with Iron-Deficiency Anemia

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This study tested the hypothesis that infants with iron-deficiency anemia show behaviors, such as increased proximity to caregivers, increased wariness or hesitance, and decreased activity, that could contribute to "functional isolation." The behavior of 52 Costa Rican 12- to 23-month-old infants with iron-deficiency anemia was contrasted with that of 139 comparison group infants with better iron status during free play and mental and motor testing and in the home. Infants with iron-deficiency anemia maintained closer contact with caregivers; showed less pleasure and delight; were more wary, hesitant, and easily tired; made fewer attempts at test items; were less attentive to instructions and demonstrations; and were less playful. Adult behavior also differed. The results indicate that iron-deficiency anemia in infancy is associated with alterations in affect and activity, suggesting that functional isolation is a useful framework for understanding poorer developmental outcome in iron-deficiency anemia, the world's most common single nutrient deficiency.

INTRODUCTION

Iron-deficiency anemia, a common nutrient disorder, has a peak prevalence among 6- to 24-month-old infants, affecting an estimated 20%–25% of the world's babies (deMaeyer & Adiels-Tegman, 1985; Florentino & Guirriec, 1984) and many low-income and minority infants in the United States (Yip et al., 1992). The issue of behavioral effects of iron-deficiency anemia has been the subject of several recent studies of human infants. (Research involving older children is reviewed in Watkin and Pollitt [in press]). Most studies focused on standardized developmental test scores as the major outcome measure, generally using the Bayley Scales of Infant Development (Bayley, 1969). Consistent results have emerged from eight studies of iron-deficient anemic infants distinguished by the use of careful definitions of iron status and the inclusion of comparison groups (Grindulis, Scott, Belton, & Wharton, 1986; Idjradinata & Pollitt, 1993; Lozoff, Brittenham, Viteri, Wolf, & Urrutia, 1982; Lozoff et al., 1987; Lozoff, Wolf, & Jimenez, 1996; Walter, de Andraca, Chadud, & Perales, 1989; Walter, Kovalskys, & Stekel, 1983; Wasserman et al., 1992). All showed that mental test scores of iron-deficient anemic infants were lower than the scores of comparison group infants before treatment (averaging 6–16 points lower), and five of seven studies reporting motor test scores found them to be lower as well (averaging 9–17 points lower).

There is limited information about behavioral differences related to iron-deficiency anemia in infancy aside from developmental test score results. Other than ratings on the Bayley Infant Behavior Record (Honig & Oski, 1984; Lozoff, Wolf, Urrutia, & Viteri, 1985; Lozoff et al., 1996; Walter et al., 1983, 1989), only two studies included direct behavioral observations. One such study did not find differences between Mexican American infants with anemia and those without during play with their mothers (Johnson & McGowan, 1983). The infants' iron status was not actually determined, although the source of their anemia was presumed to be iron deficiency. In the only other available study—a small pilot study with an 8 min free-play period, 21 Guatemalan infants with documented iron-deficiency anemia and their mothers were observed to maintain closer proximity to each other than 21 comparison group dyads (Lozoff, Klein, & Prabucki, 1986). The pattern of closer proximity was postulated to reflect alterations in affect, activity, or energy.

These observations raise the possibility that iron-deficient anemic infants are "functionally isolated." The functional isolation hypothesis, derived from research on generalized undernutrition, specifies that changes in malnourished infants' activity, affect, or attention lead them to seek less stimulation from the physical and social environments (Brown & Pollitt, 1996; Chávez & Martínez, 1975; Graves, 1978; Levitsky & Barnes, 1972; Strupp & Levitsky, 1995). In response to the infants' behavior, caregivers offer less stimulation. Over time, these alterations in child and caregiver behavior interfere with the child's normal acquisition of environmental information and adversely affect the child's development (Barrett, 1986;

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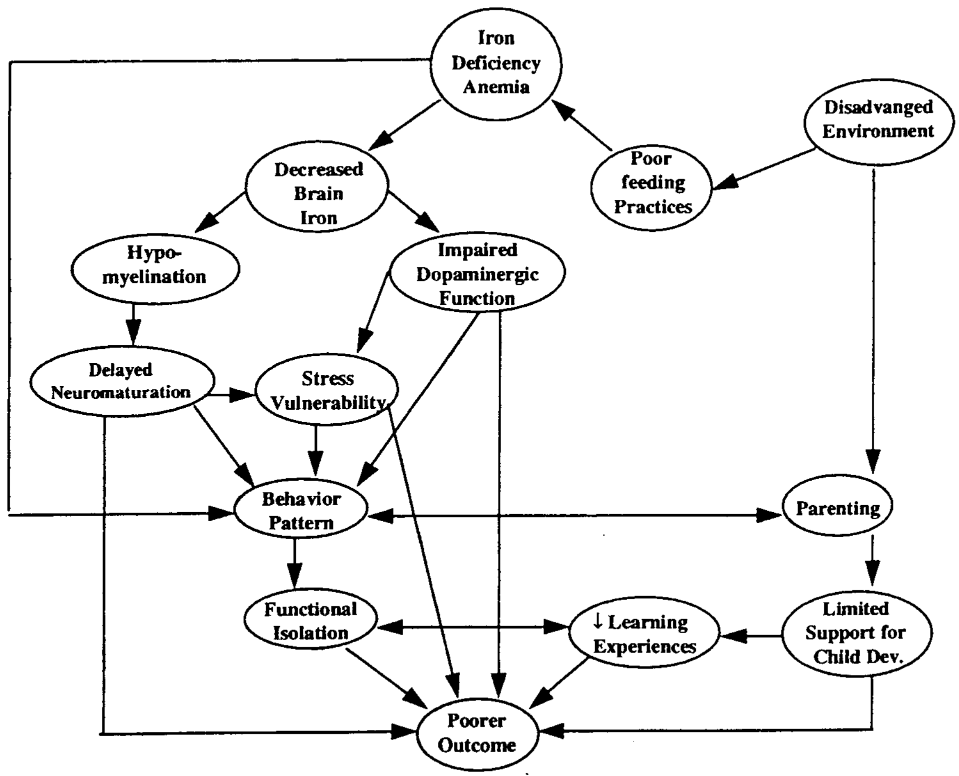

Figure 1 Conceptual model of mechanisms for poorer development in iron-deficient anemic infants. The left side of the figure focuses on the child, beginning with more biological mechanisms. The right side focuses on the environment, indicating factors that might limit support for child development. Both biological and environmental influences are shown to combine in producing poorer outcome.

Levitsky, 1979; Pollitt, Gorman, Engle, Martorell, & Rivera, 1993; Wachs, 1993).

There are several mechanisms by which early iron-deficiency anemia might produce alterations in infant behavior that would contribute to functional isolation: impaired neurotransmitter function, hypomyelination and delayed neuromaturation, and/or muscle dysfunction (for reduced motor activity). A conceptual model of these mechanisms is shown in Figure 1. Because so many central nervous system processes involve iron, one would predict that the behavioral effects of iron-deficiency anemia would be diffuse and subtle. Animal studies show such changes. For instance, when iron-deficiency anemia occurs early in development in the rat, there are lasting deficits in brain iron, electrophysiologic changes, a decrease in the number of dopamine D_2 receptors and alterations in neurotransmitter function (especially dopamine and serotonin), hypomyelination, and persisting behavioral changes that suggest an altered threshold of arousal (see summaries in Dobbing [1990]; Felt & Lozoff [1996]; Lozoff [1988]). In infants, affective changes and increased stress vulnerability would be expected with alterations in dopaminergic and serotonergic function and/or neurophysiologic maturation. Changes in activity would also be expected because of altered neurotransmitter function, hypomyelination, and/or peripheral muscle alterations. Changes in activity associated with iron-deficiency anemia have been noted in laboratory animals, human adults (see reviews by Dallman [1982]; Hunt, Zito, Erjavec, & Johnson [1994]; Lozoff & Britenham [1986]), and school-aged children (Bhatia & Seshadri, 1987). There is some recent evidence more directly implicating central nervous system alterations in iron-deficient infants. Specifically, 6-month-old babies with iron-deficiency anemia showed prolonged nerve conduction in auditory brainstem responses (Roncagliolo, Garrido, Williamson, Lozoff, & Peirano, 1996).

Environmental disadvantage is another important factor to consider. As with several other risk conditions, such as low birthweight, elevated lead levels, and generalized undernutrition, iron deficiency is associated with environmental disadvantages (reviewed in Lozoff [1990]). For instance, Costa Rican infants with iron-deficiency anemia had mothers with lower IQ scores or less education, received less stimulation in the home (reflected in lower scores on the HOME Inventory) (Caldwell & Bradley, 1984), were less likely to be breast fed, and were weaned earlier (Lozoff et al., 1987, 1996). Such disadvantageous conditions are known to have adverse effects on child development. Environmental disadvantage could contribute in another way—by limiting families' ability to provide the extra support that might be essential for developmental recovery in an infant who has had an early nutritional insult. Figure 1 shows that environmental disadvantage might adversely affect parenting behavior, which, in a transactional fashion, might combine with biologically based changes in infant behavior to produce functional isolation and poorer developmental outcome.

Although the functional isolation hypothesis seems attractive, the only available evidence that iron-deficient anemic infants show behavioral alterations comes from ratings during developmental testing, which are of questionable ecologic relevance, and from the Guatemala study, which had a small sample and only 8 min of behavioral observations during play. The present study used a much larger sample and more extensive behavioral observations to determine whether infants with iron-deficiency anemia showed alterations in affect and activity that could contribute to functional isolation. Specifically, we predicted that infants with iron-deficiency anemia would maintain closer contact with their mothers, show more wariness and hesitance in an unfamiliar setting, and be less active and energetic. Because the methodology was multifaceted, entailing behavioral ratings and direct quantitative observations during play and developmental testing and observations of behavior in the home, it was also possible to explore other behavioral differences in the infants and adults. Observations were made before and after iron therapy; behavioral change after treatment would provide convincing evidence that iron-deficiency anemia, rather than some other associated factor, was the cause of altered behavior.

This study focuses on the first steps of the functional isolation hypothesis—alterations in infant behavior and concurrent adult behavior. Other aspects of the hypothesis, such as the impact on caregiver behavior over time and the interference with normal acquisition of environmental information, require a different study design and must await testing in future studies.

METHOD

Population

The study was conducted in Costa Rica, a Central American country with an excellent record of infant health, but where iron supplementation was not routinely recommended at the time. The study consisted of door-to-door screening of an entire urban community (Hatillo, located near the capital city of San Jose), which was predominantly lower middle class. All 12- to 23-month-old infants who had been born with birthweight $\geq$2.5 kg, of singleton uncomplicated births, who were free of acute or chronic medical problems were invited to come for a physical examination and venipuncture blood sample to determine iron status (hemoglobin [Hb], transferrin saturation, erythrocyte protoporphyrin, and serum ferritin) (Cook & Finch, 1979). Eighty-five percent of those who qualified appeared for the evaluations. All those with normal physical examinations and iron measures that could be classified were asked to join the study; 10% declined. The final sample consisted of 191 infants with iron status varying from iron sufficiency (Hb $\geq$120 g/L and all three measures of iron status within the normal range) to iron-deficiency anemia (Hb $\leq$105 g/L, serum ferritin level $\leq$12 μg/L, and either erythrocyte protoporphyrin >100 μg/dL packed red blood cells or transferrin saturation $\leq$10%). These healthy infants had relatively low lead levels (M lead = 10.8 μg/dL whole blood, *range* = 5.4–21.5 μg/dL), which did not correlate with mental or motor test scores (Wolf, Jimenez, & Lozoff, 1994), and there was no evidence of growth failure or other nutrient deficiencies. Behavior and development were assessed before and after 3 months of iron therapy to determine whether any behavioral differences would be corrected. All iron-deficient anemic infants corrected their anemia with iron treatment. Attrition was 7%. Details of the original study have been published previously (Lozoff et al., 1987).

Preliminary analyses indicated that iron deficiency in the absence of anemia was not related to behavioral changes, and that infants with mild and moderate anemia were similar in behavior. Therefore, behavioral analyses compared infants with iron-deficiency anemia (n = 52) against infants with better iron status (n = 139). The anemic group was similar to the comparison group with respect to a variety of characteristics, such as sex, age, maternal age and education, and growth, but differed markedly in iron status (Table 1).

Eighty-eight percent of the infants were accompanied by their mothers. The remainder were accompanied by another family member, always a familiar

Table 1 Characteristics of Child and Family

	Infants with Iron-Deficiency Anemia (n = 52)	Comparison Group (n = 139)
Sex (male)	62%	53%
Age (months)	16.5 ± 2.9	17.4 ± 3.3
Birthweight (kg)	3.21 ± .45	3.32 ± .43
Birth order	2.1 ± 1.2	2.5 ± 2.5
Weight (kg)	10.6 ± 1.3	10.7 ± 1.2
Length (cm)	78.5 ± 3.9	79.4 ± 3.9
Weight-for-length percentile	54.1 ± 25.8	49.8 ± 28.7
Head circumference (cm)	46.5 ± 1.2	46.3 ± 1.6
Hemoglobin (g/dL)	9.52 ± .89	12.21 ± .91***
Serum ferritin (μg/L)	3.3 ± 2.3	9.4 ± 9.5***
Erythrocyte protoporphyrin (μg/dL red blood cells)	325.5 ± 177.2	101.3 ± 59.1***
Transferrin saturation (%)	9.4 ± 3.7	16.4 ± 7.2***
Maternal age at child's birth	24.8 ± 4.8	25.6 ± 5.8
Maternal education (years)	8.5 ± 2.8	8.9 ± 2.9

Note: Values are means ± 1 *SD*.
*** $p < .001$.

caregiver. The pattern of results remained unchanged regardless of whether data from all children were analyzed or only from those whose mothers were present. Therefore, the results presented here include the entire sample.

Procedure

Observations in a standard setting. Behavioral observations were performed in a clinic testing room before treatment and after 3 months of appropriate therapy. Neither the caregivers nor the tester were aware of the children's hematologic status or treatment group until the study was completed.

Each infant and accompanying caregiver were videotaped in a 15 min free-play situation prior to developmental evaluation with the Bayley Scales of Infant Development (Bayley, 1969). The observation room contained a table, two chairs, a playpen, a small staircase, a walking board (parts of the Bayley test), and a set of toys (a train pull-toy, a ball, a play phone, a wind-up music radio, and four pictures on the wall). To permit a crude estimate of motor activity, the floor was marked with tape, creating a grid of 1 m squares. The infants were also videotaped during developmental testing.

Behavioral coding. Through continuous coding of behavior, the frequency, duration, and sequence of infant and maternal (and tester) behaviors in real time were recorded (Stephenson & Roberts, 1977; Stephenson, Smith, & Roberts, 1975). The coding systems for the play sessions and the mental and motor test sessions shared the same general framework, with differences in specific codes depending on the situation (Lozoff et al., 1986). Each coding system included the following categories: (1) the spatial relations between infant and caregiver (e.g., body contact, close proximity without touching, beyond arm's length); (2) the affective state of the infant (e.g., wary versus engaged, smiles/laughs, cries/fusses); (3) the behavior of the infant in relation to toys, test materials, and the adults present; and (4) the behavior of caregiver (and tester) in play or testing (e.g., attempts to engage infant, smiles/laughs, item presentation/demonstration). Codes in the first two categories generally consisted of sets of mutually exclusive and exhaustive descriptors of behavior with both frequency and duration. Codes in the last two categories were primarily momentary in nature, recorded by frequency only. Complete descriptions of codes and coding instructions are available from the authors.

Trained observers, uninformed regarding each infant's hematologic status, coded the videotapes using small lap-top portable computers (Radio Shack, Model 100 series). Before coding the study videotapes, the coders were trained with practice videotapes that were not part of the final sample. A randomly selected subset of 10% of study videotapes was then coded independently by both observers prior to starting each set. The intraclass correlations averaged .88–.93 in the three sessions (play, mental, and motor). Reliability checks were made throughout coding on another random 10% of the tapes. Levels of agreement remained at or above the initial levels.

Behavior ratings during developmental testing. The behavior of the infants during developmental testing was also characterized by ratings on the Infant Behavior Record (IBR, the third component of the Bayley Scales) (Bayley, 1969). Two approaches to IBR analysis were combined to generate summary scores, one which characterized an infant's affect during testing and another which described the infant's orientation to tasks. These analytic approaches, which make the IBR more clinically useful, were: (1) factor analytic techniques identifying IBR scales that cluster together, regardless of age, sex, or culture (Matheny, 1980; Van der Meulen & Smrkovsky, 1982), and (2) an analysis of normative U.S. samples identifying IBR ratings to be suspected as abnormal because they reflect behavior that is poorly adaptive in the test situation and observed relatively infrequently in normal children (Wolf & Lozoff, 1985). There was a single tester for all the Bayley tests, and information on reliability for her IBR ratings is not available.

The quality of the mother's participation during the mental and motor test was also rated, using 3 to 5 point Likert scales. The scales assessed emotional expressiveness, demonstration of affection, sensitivity to the child's state, encouragement of achievement, handling of the child, patience/tolerance, and degree of involvement. These scales (available from the authors) were developed to rate maternal behavior during developmental testing, but we were guided by several approaches in studies of mother-infant interaction under other conditions (Farran et al., 1987; Mahoney, Powell, & Finger, 1986). The ratings were made from videotape by two U.S. raters, who maintained 88%–91% agreement throughout (exact agreement on 3 point scales and within 1 point on 5 point scales).

Observations in the home. Observations during developmental testing and play are inadequate to characterize the everyday behavior of infants. To offset the limitation and artificiality of this sample of behavior, study personnel (trained psychologists) also made observations in the home in conjunction with visits to monitor the children's medication. Only a brief observation was feasible, however, given the number of infants in the study and the need to make daily visits over a 3 month period to insure intake of iron therapy. Upon arrival, the home visitors recorded a "snapshot" of the infant's and caregivers' behavior and activities (Rogoff, 1978). Specifically, the baby's state, location, distance from mother, and activity were noted, as well as caregivers' identity and activities in relation to the infant. A weekly summary, totaling a given week's observations in each category and dividing by the number of days with data, was used in analysis. The first week gives an indication of pretreatment behavior; the final week (week 13, on average) reflects behavior after all children's anemia had been corrected with iron therapy.

Statistical Analysis

The first phase of data analysis was to test our predictions that anemic infants were more hesitant and wary, less active, and more likely to maintain close contact with their caregivers during play, developmental testing, and at home. Anemic infants were contrasted with the comparison group, using two-tailed tests of significance for the Student t test for independent means in comparisons involving continuous variables, and the chi-square test for variables with distributions that made categorical analysis more appropriate. A .05 level of significance was selected, given the hypothesis-testing, confirmatory nature of these analyses. With 24 comparisons related to affect, proximity, and activity, approximately one would be expected to be significant by chance alone.

The second phase of analysis was exploratory. To determine if the behavior of anemic infants and adults differed in other ways during play and developmental testing, we used MANOVA techniques, grouping the remaining behavioral measures from videotape coding into four sets: other infant behavior during play, infant test-taking behavior, maternal behavior, and tester behavior. If the MANOVA indicated a significant difference for a particular set, the behaviors comprising that set were tested individually, with adjustment of the alpha level for the number of comparisons involved. The spot observations in the home, however, did not readily suggest such a priori groupings. Therefore, a three-factor, varimax-rotated factor analysis was performed, and the anemic and comparison groups were compared on their factor scores.

In accord with the conceptual framework presented in Figure 1, iron-deficiency anemia and any associated alterations in infant behavior were expected to be imbedded in the context of less advantaged environment. To provide further information on the relation of other factors to behavioral differences, we considered the potential effects of 11 control variables that might influence behavior—six concerning infant characteristics, growth, and feeding (age, sex, birth order, birthweight, weight-for-height percentile, weeks of breast feeding) and five related to family environment (father absence, maternal age, education, and IQ [Wechsler, 1981], and total score on the HOME Inventory [Caldwell & Bradley, 1984]). We began with the assumption that a control variable could not be the true cause of an observed relation between iron-deficiency anemia and infant behavior unless the control variable related to the behavior in question (Schlesselman, 1982). Zero-order correlations of these variables with each of the behavioral outcome measures were used to identify variables that should be considered in multivariate analyses to control for confounding. Each behavioral variable was evaluated in a multiple regression analysis including iron-deficiency anemia and all control variables even weakly ($p < .10$) related to it.

Posttreatment analyses focused on the pretreatment behavioral differences, comparing the formerly anemic children with the rest of the sample. All statistical analyses were performed using Systat (Wilkinson, 1990).

RESULTS

Behavior of Iron-Deficient Anemic Infants before Treatment

The videotaped play sessions were of similar length for both the iron-deficient anemic infants and the rest of the sample (14.9 ± 0.2 min versus 14.9 ± 0.4 min). The Bayley mental test was also of similar duration in the two groups (27.7 ± 8.0 min versus 27.4 ± 6.7 min). However, the motor tests were substantially shorter for the iron-deficient anemic group (12.7 ± 4.9 min versus 15.5 ± 4.9 min for the comparison group), $t(1, 186) = 3.54$, $p < .001$. To take this difference into account, we report motor test behaviors with duration in terms of proportion of test time. Key findings are summarized below. Statistical information provided in Tables 2 and 3 is not repeated in the text.

Comparisons Related to the Functional Isolation Hypothesis

Spatial relations and activity (Table 2). During both play and motor testing, when infants were free to move about, those with iron-deficiency anemia were more likely to stay close to their caregivers. In the play session, a greater proportion of infants with iron-deficiency anemia never played at a distance beyond arm's length from the caregiver (23% versus 10% of the comparison group). During the motor test, infants with iron-deficiency anemia spent a smaller proportion of the motor test at a distance from their caregiver. They ventured beyond arm's length less often (2.2 ± 2.2 times versus 3.1 ± 2.3 times for the rest of the infants), $t(1, 186) = 2.59$, $p = .01$.

For the play session, we created a composite measure that considered together how often infants changed their proximal relations to their mothers and how often they vocalized, because infants can actively create opportunities for interaction with the social and physical environment with either type of behavior. Using the means for the sample to determine "high" and "low," infants were separated into four categories: high vocalization/high proximity change, high vocalization/low proximity change, low vocalization/high proximity change, low vocalization/low proximity change. More anemic infants were in the low vocalization/low proximity change category (44% versus 28% of the comparison group). In keeping with this observation, there was also some indication that anemic infants were less physically active than the other infants. During play, there were suggestive trends indicating that they played in fewer areas of the room, $p = .06$, and crossed floor gridlines fewer times, $p = .09$. During the mental test, the anemic infants showed less physical, restless activity. During the motor test, there was a suggestive trend that fewer of them fell down.

Infant affect (Table 2). During the motor test, infants with iron-deficiency anemia were more wary and hesitant than the other infants. Specifically, 25% of them remained hesitant for the entire motor test, never becoming engaged in the test situation, compared to 10% of the comparison group. There were few differences between infants with iron-deficiency anemia and those in the comparison group on quantitative codes of affect during play or mental testing. There was virtually no distress during play in either group, and one of five infants in each group remained hesitant or wary throughout the mental test. However, the iron-deficient anemic infants showed less delight during the mental test.

On the Bayley Infant Behavior Record, there was a suggestive trend, $p = .06$, indicating that more of the anemic group than the comparison group was rated as abnormal in overall affect; this relation became statistically significant after control for confounding variables. The five scales in the Test-Affect factor were examined individually to see if any particular behaviors accounted for the increase. Scale 13, Endurance, differentiated the groups; 42% of iron-deficient anemic infants received suspect ratings, indicating easy fatigability, compared to 19% of the comparison group. There were also suggestive differences on Scale 2, indicating less responsivness to the examiner. There were no differences in the Task-Ori-

Table 2 Behaviors Related to Functional Isolation: Spatial Relations, Activity, and Infant Affect before Treatment

	Iron-Deficiency Anemia[a] (n = 52)	Comparison Group (n = 137)[a]	Test Statistic	Multiple Regression[b]
Infant-mother proximity:[c]				
Child-initiated close contact in play (min)	4.8 ± 3.0	5.1 ± 3.3	$t(1, 187) = .67$	age
Infant never goes beyond arm's length in play (%)	23	10	$\chi^2 = 5.25^{*}$	age
Child-initiated close contact in motor test (%)[d]	11 ± 14	13 ± 18	$t(1, 186) = .88$	
Child-initiated arm's length distance in motor test (%)	22 ± 23	31 ± 25	$t(1, 186) = 2.18^{*}$	age
Low proximity change/low vocalization (%)	44	28	$\chi^2 = 4.69^{*}$	age
Physical activity:				
Areas explored in play (n)	3.6 ± 1.2	3.9 ± 1.2	$t(1, 179) = 1.91^{-}$	
Crossing floor grid lines in play (frequency)	18.6 ± 18.0	23.3 ± 15.7	$t(1, 179) = 1.71^{-}$	age, sex[e]
Physical, restless activity in mental test (s)	19.2 ± 35.0	37.8 ± 90.3	$t(1, 187) = 2.04^{*}$	
Off mother's lap in mental test (s)	34.3 ± 100.5	27.3 ± 74.1	$t(1, 73) = -.46$	age
Falls down in motor test (%)	33	48	$\chi^2 = 3.49^{-}$	
Infant affect (behavior codes):				
Delight, laughter (frequency):				
Play	1.3 ± 2.0	1.9 ± 2.8	$t(1, 132) = 1.49$	
Mental test	3.2 ± 3.6	4.6 ± 5.6	$t(1, 144) = 2.09^{*}$	
Motor test	.6 ± 1.7	.8 ± 1.8	$t(1, 186) = .58$	
Crying, whining, fussing (frequency):				
Play	1.6 ± 4.6	1.2 ± 2.6	$t(1, 64) = -.57$	
Mental test	4.6 ± 9.7	8.2 ± 28.1	$t(1, 186) = 1.32$	
Motor test	4.8 ± 5.0	5.3 ± 5.9	$t(1, 186) = .57$	birth order
Remains wary, heistant throughout:				
Mental test (%)	21	21	$\chi^2 = .00$	sex
Motor test (%)	25	10	$\chi^2 = 7.53^{**}$	
Infant affect: Infant Behavior Record (% suspect ratings):				
Scale 2. Responsiveness to examiner (%)	29	19	$\chi^2 = 1.96$	age[f]
Scale 5. Fearfulness (%)	37	34	$\chi^2 = .12$	
Scale 6. Tension (%)	29	24	$\chi^2 = .38$	
Scale 7. Happiness (%)	27	22	$\chi^2 = .61$	birth order
Scale 13. Endurance (%)	42	19	$\chi^2 = 10.39^{***}$	
Abnormal affect (2 of 5 ratings in the suspect range)	42	28	$\chi^2 = 3.54^{-}$	[g]

[a] Because of technical problems, videotapes of two children were missing for play and mental test and of three children for the motor test.

[b] Unless indicated, effects of iron-deficiency anemia given for univariate analyses remained statistically significant or suggestive after control for background factors. Background factors with statistically significant effects are shown.

[c] All infants were accompanied by a familiar caregiver, referred to as "mother" here. There were no proximity codes for the mental test because infants were generally on their mothers' laps for the entire test.

[d] Proximity codes are expressed as proportion of total test time for the motor test because the duration of the tests differed between the anemic and comparison groups.

[e] After control for other factors, the effect of iron-deficiency anemia was neither statistically significant nor suggestive.

[f] After control for other factors, the effect of iron-deficiency anemia showed a suggestive trend.

[g] After control for other factors, the effect of iron-deficiency anemia became significant ($p < .05$) rather than suggestive.

$^{*} p < .05$; $^{**} p < .01$; $^{***} p < .001$; $^{-}$ suggestive trend ($p < .10$).

entation summary measure or in the four individual scales that made up that composite.

Effects of Potential Confounding Variables

Infant characteristics and growth related to several of the behavioral measures, but controlling for these influences changed the findings only slightly, whether in comparisons directed at the functional isolation hypothesis or exploratory analyses (see below). In contrast, factors related to family environment did not generally show statistically significant relations with infant behavior when entered in multiple regressions. The notable exception was that both

Table 3 Other Behavioral Differences between Anemic and Comparison Groups before Treatment

	Iron-Deficiency Anemia[a] ($n = 52$)	Comparison Group ($n = 137$)[a]	Test Statistic	Multiple Regression[b]
Infant test-taking behavior				
(MANOVA $F(11, 176) = 1.95$, $p = .04$[c]):				
Attempts mental tasks (frequency)	61.0 ± 19.4	69.1 ± 18.7	$t(1, 187) = 2.66$**	age, mother's IQ[d]
Attempts motor tasks (frequency)	17.1 ± 11.3	25.8 ± 14.6	$t(1, 186) = 3.87$***	age
Pays attention to tester request (frequency)	16.0 ± 9.5	20.4 ± 9.3	$t(1, 186) = 2.93$**	age
Plays with motor test material (frequency)	5.1 ± 4.0	7.0 ± 4.8	$t(1, 186) = 2.56$**	age
Maternal behavior[e]				
(MANOVA $F(14, 173) = 2.61$, $p = .002$[f]):				
Initiates interaction in play (frequency)	12.6 ± 8.6	9.1 ± 7.5	$t(1, 187) = -2.81$**	age
Delight, laughter in play (frequency)	1.3 ± 1.6	2.8 ± 3.8	$t(1, 185) = 3.98$**	
Demonstrates/encourages motor tasks (frequency)	10.2 ± 11.4	15.4 ± 12.6	$t(1, 186) = 2.59$**	age
Tester behavior				
(MANOVA $F(6, 181) = 2.29$, $p = .04$[g]):				
Motor item presentation/encourage (frequency)	26.8 ± 14.8	32.4 ± 14.7	$t(1, 186) = 2.32$*	age
Different motor tasks (number)	7.7 ± 3.8	9.5 ± 3.5	$t(1, 186) = 3.23$***	age

[a] Because of technical problems, videotapes of two children were missing for play and mental test and of three children for the motor test.
[b] Unless indicated, effects of iron-deficiency anemia given for univariate analyses remained statistically significant or suggestive after control for background factors. Background factors with statistically significant effects are shown.
[c] To keep overall alpha levels at .05, the significance level for each MANOVA was set by dividing .05 by the number of comparisons. For infant test-taking behavior, there were 11 behaviors tested individually, considering $p < .005$ and $p < .01$ as significant or suggestive, respectively.
[d] After control for other factors, the effect of iron-deficiency anemia was neither statistically significant nor suggestive.
[e] All infants were accompanied by a familiar caregiver, referred to as "mother" here.
[f] Fourteen behaviors tested individually, considering $p < .005$ and $p < .01$ as significant or suggestive, respectively.
[g] Six behaviors tested individually, considering $p < .01$ and $p < .05$ as significant or suggestive, respectively.
* $p < .05$; ** $p < .01$; *** $p < .001$.

infant age and mother's IQ were related to the number of attempts infants made on the mental test, and anemia no longer showed a statistically significant relation after control for these factors (see below). The number of attempts on the motor test, however, was unrelated to family characteristics, and the effect of anemia remained significant in the regression analysis. Tables 2 and 3 indicate the control variables that were significant in multiple regression analyses.

Exploratory Analyses

Three of the MANOVA analyses (infant test-taking behavior, mother behavior, and tester behavior) showed statistically significant differences between the anemic infants and the comparison group. To understand the nature of the differences, we examined the individual behaviors in each set, using alpha levels of .05 divided by the number of comparisons to maintain the overall significance level for each set at .05. Comparisons that were statistically significant or suggestive at these stringent levels are shown in Table 3 and summarized below.

During both the mental and motor tests, iron-deficient anemic infants made fewer attempts to perform test items than did infants in the comparison group. During the motor test, iron-deficient anemic infants were less likely to attend to instructions and demonstrations. There was also a suggestive trend that the iron-deficient anemic infants played with toys and equipment during the motor test less often than did comparison group infants.

On specific comparisons of maternal behavior during play, the caregivers of iron-deficient anemic infants initiated interaction more frequently than did caregivers of the rest of the infants. However, caregivers of anemic infants laughed less, showing less obvious pleasure in their child. During the motor test, there was a suggestive trend that caregivers of iron-deficient anemic infants were less likely to demonstrate the desired motor behavior or to use physical or verbal encouragement for their children to perform the tasks.

On the ratings of maternal behavior during mental and motor testing, the only difference related to demonstration of affection. During both parts of developmental testing, a smaller proportion of the mothers of iron-deficient anemic infants was considered to be highly affectionate, compared to mothers of infants in the comparison group: mental test, 5% versus 23%, $\chi^2(1, N = 162) = 6.43$, $p = .01$; motor test, 5% versus 21%, $\chi^2(1, N = 161) = 5.28$, $p = .02$. Maternal iron deficiency was not the explanation for differences in caregiver behavior, however, because only six of the mothers in the entire sample had iron-deficiency anemia.

There was also evidence that the tester behaved differently with anemic and comparison group infants. Individual comparisons indicated that differences occurred during the motor test, rather than throughout the Bayley. During the motor test, there was a suggestive trend indicating that the tester made fewer attempts to elicit the motor skills of anemic infants (fewer demonstrations and encouragements). Fewer different motor tasks were administered to iron-deficient anemic infants, although the number of Bayley items actually scored was comparable.

The "snapshot" observations of behavior in the home, recorded by project psychologists upon arrival to monitor medication, were analyzed by factor analysis. Iron-deficient anemic infants differed from the comparison group on two of the three factors. They were higher than the comparison group on the first factor (.25 ± 0.94 versus −.10 ± 1.00 for the comparison group), $t(1, 181) = -2.15$, $p < .05$. This factor had loadings primarily related to affect and proximity; the higher score for anemic infants indicates that they were more likely to be asleep, irritable, doing nothing, being carried, or in bed and less likely to be on the patio or playing interactively with objects. The anemic group was lower on the second factor (−.24 ± .86 versus .09 ± 1.04 for the comparison group), $t(1, 181) = 2.05$, $p < .05$. This factor had loadings primarily related to activity; the lower score for anemic infants suggests that they were less likely to be walking, playing interactively without objects, within arm's length of the mother, or outside in the yard and more likely to be sitting on the floor, at a distance from the mother, engaged in solitary activity. The third factor, which included behaviors that seemed primarily related to eating, did not show differences (−.03 ± 1.01 versus .01 ± 1.00 for the comparison group), $t(1, 181) = 0.24$, *ns*. In addition to these factor analyses, two behaviors with very skewed distributions were analyzed categorically. A greater proportion of the anemic group was being carried on more than 1 day: 57% versus 36%, $\chi^2(1, N = 183) = 6.34$, $p < .01$. They were also more likely to be in a playpen at some visit: 29% versus 12%, $\chi^2(1, N = 183) = 7.82$, $p < .01$.

Behavior of Iron-Deficient Anemic Infants after Treatment

After 3 months of treatment, behavioral differences between the formerly anemic and comparison groups were observed primarily during the Bayley motor test and spot observations in the home. During the motor test, formerly anemic infants continued to spend a lower proportion of test time at a distance from their caregivers (27% ± 23% of time versus 36% ± 25% of time for other infants), $t(1, 179) = 2.07$, $p = .04$. The formerly anemic group still made fewer attempts to do motor tasks (23.6 ± 11.1 attempts versus 27.6 ± 13.1 attempts for the comparison group), $t(1, 179) = 1.93$, $p = .05$. Again, fewer different motor tasks were presented to them (9.6 ± 1.9 tasks versus 10.3 ± 2.5 tasks for the comparison group), $t(1, 115) = 2.09$, $p = .04$. However, in contrast to findings at the pretreatment assessment, the motor tests of formerly anemic infants were not shorter (14.2 ± 3.9 min versus 14.6 ± 3.7 min for the comparison group), $t(1, 179) = 0.66$, *ns*, and the tester did not make fewer attempts to elicit their motor skills (34.5 ± 13.0 times versus 35.6 ± 13.4 times for the comparison group), $t(1, 179) = 0.48$, *ns*.

Spot observations in the home showed that formerly anemic infants continued to differ in behavior, especially on the first factor, $t(1, 176) = 1.98$, $p = .05$, indicating that they were more likely to be crying, irritable, asleep, doing nothing, or in a playpen and less likely to be outside the house or quietly engaged or playing interactively.

The only other difference was in maternal affect: the caregivers of formerly anemic infants laughed less often during play, showing obvious pleasure in their child less frequently (1.8 ± 2.0 times versus 3.1 ± 3.5 times for caregivers of other infants), $t(1, 150) = 3.20$, $p = .002$.

DISCUSSION

The pattern of pretreatment results in this study supports the hypothesis that infants with iron-deficiency anemia show behaviors that could contribute to functional isolation. Iron-deficient anemic infants maintained closer contact with caregivers during play and motor testing. They showed less pleasure/delight in the mental test, and more of them were wary or hesitant throughout the motor test. More iron-deficient anemic than comparison group infants received IBR ratings indicating little endurance and excess fatigability, and there were other indications that they were less active. During play, they were more likely to be low both in vocalization and in changes in proximity to their mothers, thus creating fewer opportunities for interaction. In addition, observations in the home showed that iron-deficient anemic infants were more likely to be carried by their mothers, asleep, irritable, alone in a playpen, or doing activities that did not involve interaction with caregivers.

These findings seem to fit with other research, even though there is nothing directly comparable to the study's quantitative analyses during developmental testing and observations in the home. Our results are consistent with previous IBR ratings indicating affective changes among iron-deficient infants during Bayley testing, such as increased fearfulness, wariness or hesitance, unhappiness, or tension (Honig & Oski, 1984; Lozoff et al., 1985, 1996; Walter et al., 1983, 1989), and with an earlier pilot study indicating closer proximity to caregivers during play (Lozoff et al., 1986). Such behaviors could make it more difficult for iron-deficiency anemic infants to learn from their environments. Even though closer contact of iron-deficient anemic infants and their caregivers may be appropriate, given the children's vulnerability, there may be some negative effects. Part of developing cognitive, motor, and social skills in infancy depends on achieving a balance between staying close to caregivers and venturing away to try new things and to learn from falls and failures.

This study also shows that both the tester and primary caregivers related differently to infants with iron-deficiency anemia. In play, the caregivers of iron-deficient anemic infants showed less obvious pleasure in the child, even though they initiated interaction more often. They showed less affection during both mental and motor testing. During motor testing, both the caregiver and the tester tried less frequently to get the iron-deficient anemic infants to perform the tasks, and the motor test sessions were shorter for them. It is unlikely that this differential treatment was due to knowledge of which children were anemic. Neither the caregivers nor the tester were informed of the children's hematologic status or treatment group until the study was completed, and even the project pediatrician was unable to identify anemic children accurately on the basis of physical findings. However, it is possible that adults perceived the iron-deficient anemic babies as less able to cope with the testing situation or other unfamiliar, somewhat stressful experiences. Thus, the adults may have appropriately recognized the children's fearfulness and hesitance or their fatigue and not wanted to push them too hard.

Alternatively, less expressiveness in the mothers of iron-deficient anemic children may reflect depressed mood. After this study was completed, we became aware of a link between maternal depressive symptoms and another nutritional deficiency disorder—generalized undernutrition (reviewed in Salt, Galler, & Ramsey [1988]). Because the adverse effects of maternal depression on child outcome are being increasingly recognized, we collected data on maternal depression upon follow-up when the children were 5 years old (unpublished data). There were no differences between anemic and comparison groups with respect to current depressive symptomatology or lifetime diagnosis of depression, but we have no information on maternal depression during the period when the behavioral observations were made. However, the fact that the tester also behaved differently with the anemic infants suggests that infant behavior was eliciting different adult responses more generally. Nonetheless, assessing maternal depression will be important in future studies related to the functional isolation hypothesis, whether in relation to generalized undernutrition or iron-deficiency anemia.

In this study, all of the iron-deficient anemic infants corrected their anemia with 3 months of iron therapy. However, iron treatment did not appear to correct all the behavioral differences. This may be a parallel to findings about mental and motor test scores. Lower developmental test scores have still been observed after treatment in the majority of anemic infants in four studies involving a full course of iron therapy (Aukett, Parks, Scott, & Wharton, 1986; Lozoff et al., 1987, 1996; Walter et al., 1989). (One other study reported correction of lower scores [Idjradinata & Pollitt, 1993].) Developmental differences seem to be long-lasting. The little available longitudinal data show that children who were anemic as infants still test lower in mental and motor development years later (Dommergues et al., 1989; Lozoff, Jimenez, & Wolf, 1991; Palti, Meijer, & Adler, 1985; Palti, Pevsner, & Adler, 1983; Walter, de Andraca, Castillo, Rivera, & Cobo, 1990) and show functional impairment in school at age 12 (lower achievement test scores [Lozoff, Wolf, Mollen, & Jimenez, 1997], need for special education [Hurtado, 1995]).

An important limitation of this study is that the behavioral alterations cannot be unequivocally attributed to iron-deficiency anemia. Had this study shown that iron therapy corrected behavioral differences, there would have been more certainty that iron-deficiency anemia was the cause (Lozoff, 1990).

However, persisting effects could still be due to iron-deficiency anemia if, as animal studies suggest, iron-deficiency anemia during maximal brain growth has effects on brain and behavior that are not reversed with treatment. Alternatively, some associated factor, such as maternal depression or other environmental disadvantage, could account for both poor infant feeding practices (leading to iron-deficiency anemia) and lack of stimulation (leading to altered behavior and development). Although we statistically controlled for such factors, this approach does not address the problem satisfactorily. Available measures of these environmental factors are quite crude and may miss meaningful differences in the childrearing environment. More importantly, many biological insults are more common in disadvantaged environments, and statistical methods that "remove" the effects of environment may lead to an underestimation of the impact of the biological stressor and / or distort the reality of children's lives.

The observations of behavior in this study, although much more extensive than in previous studies, are still limited. Details come primarily from 15 min of play and about 45 min of developmental testing at each assessment. The daily observations in the home provide more ecologically valid information and occurred over 3 months, but they nonetheless provide only a snapshot of the infant's behavior each day.

Another concern with this study, as with any other, is whether the results can be generalized. In this study, the sample was carefully selected to exclude infants with conditions that could adversely affect behavior, such as low birthweight or illness, and this group of Costa Rican infants was growing normally by U.S. standards. Thus, the results are most generalizable to term, healthy infants who are free of generalized undernutrition. These conditions apply to many children in industrial countries, but most infants in developing countries do not have as optimal growth and health as the sample here. The effects of iron-deficiency anemia under less healthy conditions are as yet unknown, but it seems reasonable that they might be more adverse.

In sum, the available evidence confirms the hypothesis that iron-deficient anemic infants show alterations in activity and affect that could limit the stimulation they seek and / or receive from the physical and social environment. Despite limitations in our ability to attribute causality and to understand the underlying mechanisms, the research has important practical implications. Infants with iron-deficiency anemia may require special intervention in addition to iron therapy. Intervention, such as stimulation programs, would ideally be targeted toward the specific behavioral alterations of infants with iron-deficiency anemia and at the special needs of their families. Even more important, preventing iron-deficiency anemia might help foster the behavior and development of disadvantaged infants throughout the world.

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