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IRON DEFICIENCY AND COGNITIVE FUNCTION

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The intent of this review is to determine whether iron deficiency (ID) is a developmental risk factor as defined by an increment in the probabilities of a deviation from a normal developmental trajectory. The data available from published reports have been used selectively, as most studies that are cited had an experimental or quasi-experimental research design with a focus on causality. A broader view, including discussion of methods and research designs and descriptions of particular studies, is available elsewhere (8, 31, 33, 48).

Among the many different pathways through which iron deficiency can affect cognition (see Table 1) are two that have been most frequently discussed. Briefly, one proposes that even at the very early stages of iron deficiency, a decrement in iron-dependent dopamine D2 receptors in the cortex alters dopamine neurotransmission, which, in turn, impairs cognitive function (16, 45, 48–50). The alternative hypothesis is less explicit and refers to more advanced stages of iron deficiency when hemoglobin concentration is com-

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Table 1 Areas of possible impact of iron deficiency on the central nervous system[a]

General biochemical	Specific sites	Impact
Heme synthesis	1. Porphyrin synthesis (general ↓; ↑ FEP)	Toxic or intracellular deficiency
	2. Mitochondrial cytochromes (c, oxidase)	Respiration, oxidative phosphorylatio
	3. Microsomal cytochromes (P_{450}, b_5)	Toxic
Krebs cycle	Succinate dehydrogenase (Fe-S flavoprotein), aconitase (Fe cofactor)	Respiration
Fe-S flavoproteins	NADH-ubiquinone reductase, α-GP dehydrogenase	Respiration, oxidative phosphorylatio
Nucleic acids	DNA synthesis, mitosis	Brain growth
Catecholamines	Phenylalanine hydroxylase, tyrosine hydroxylase, monoamine oxidase	Neurotransmitter levels
Serotonin	Tryptophan pyrrolase, tryptophan hydroxylase, aldehyde oxidase	Neurotransmitter levels
Folic acid/B_{12}	Formimino transferase, THF methyltransferase	

[a] Source: Reference 17.

promised. It postulates that in the presence of anemia there may be systemic effects that interfere with cognition (16). Neither hypothesis has been validated; however, most research in this area has focused on dopamine neurotransmission.

The following review is divided into four sections. First I discuss some issues of definition regarding both predictor (i.e. iron deficiency) and outcome (i.e. cognition) variables. Next, I discuss the associations that have been reported for iron deficiency anemia (IDA) without addressing the issue of causality, which is covered in the third section. The review ends with an attempt to make explicit the nature of the cognitive alterations found among children with IDA.

DEFINITION OF PREDICTOR AND OUTCOME VARIABLES

Iron Deficiency

The requirement for use of multiple indicators (e.g. ferritin, erythrocyte protoporphyrin, hemoglobin) in the definition of iron deficiency is no longer an issue among investigators concerned with the functional effects of ID. Presently, there is no valid substitute for such an approach, because none of

the indicators can monitor the entire spectrum of iron deficiency. Multiple indicators increase the sensitivity of the diagnosis and reduce the risk of sample heterogeneity in studies on functional effects (3, 10, 17, 35, 47).

The studies cited in the following review included no less than two iron indicators to establish iron class and generally relied on the standard cut-off points to define deficiency. In some instances the sensitivity and specificity of the criteria for IDA were tested by a comparison of the class criteria with the hemoglobin response to iron therapy (14, 22). In all cases the dose in iron therapy was adjusted according to the age and weight of the children.

A main concern of investigators today is to define the course of the deficiency from its onset to the time when it is first identified. Its duration and changes in severity, in addition to its timing (i.e. developmental period when present), are likely to play the role of effect modifiers (20, 34). At present, however, no exact methodologies and ethically acceptable research designs are available to directly measure duration and timing. Based on the pathophysiology of iron deficiency, an estimate of its duration is indirectly derived from its severity. A promising option to estimate duration is the use of prospective research protocols that identify new cases in the same cohorts of children within pre-established time periods.

Cognitive Variables

Investigators agree on the need to establish the effect of ID on "mental development" or cognition, broadly defined. Because the most complex postnatal neural changes that take place in the human brain occur during the first two years of postnatal life, the infant's development is thought to be particularly vulnerable to ID (5, 6, 9, 15, 50). This assumption is partly supported by experimental work with protein and calorie restrictions of laboratory animals during the lactation period that resulted in permanent structural changes in the central nervous system (9). ID in rodent pups results in a deficit in the availability of iron in the brain, which persists following the saturation of iron stores (5, 6).

Investigators working with infants prefer to use the Bayley Scales of Mental and Motor Development (BSMMD[1]), while those working with preschoolers

[1]The Bayley Scales of Mental and Motor Development are standardized instruments that sample different categories of behaviors in infants from 2 to 30 months. The Mental scale yields an aggregate score, the Mental Development Index (MDI) with a mean of 100 and a standard deviation of 16 MDI points. This scale characterizes the behavioral development of infants with samples of different mental functions such as memory, learning, and vocabulary. The Motor scale yields the Psychomotor Development Index (PDI), with the same mean and standard deviation as the MDI, This scale samples gross and fine motor skills.

The Infant Behavior Record is the third component of the Bayley Scales. This rating scale assesses different emotional and motivational expressions of the child during testing.

and school-age children have chosen IQ tests [e.g. Wechsler Intelligence Scale for Children (WISC), Raven's Progressive Matrices[2]], learning tasks (e.g. discrimination and oddity learning), and school achievement measures. Presumably, the psychological construct that lies behind these outcomes from studies with different age groups remains constant from infancy to late childhood. However, such an assumption is supported neither by theory nor by empirical data.

While the names of these tests used in studies on infants and older children might suggest otherwise, the scales of mental (e.g. BSMD) development used among children during the first two years of life and the intelligence and cognitive tests used among preschool and school age children tap different constructs. On one hand, the BSMD (2) intends to characterize the behavioral repertoire of an infant at a particular age, with a disclaimer that this characterization is a reflection of intelligence or mental competence. On the other hand, the intelligence tests (e.g. WISC) and the learning tasks used with older children intend (with different degrees of success) to scale children within a spectrum of mental ability (2, 30). This difference in the nature of the tests is discussed below in more detail, as it is pertinent to our understanding of the nature of the effects that have been reported. If such differences in the very nature of the tests used do exist, why is there such remarkable consistency in the findings across studies with different age groups? A valid answer to this query, in my view, will place us very close to an understanding of the functional effect of iron deficiency.

ASSOCIATIONS BETWEEN DEFICIENCY AND BEHAVIORAL ALTERATIONS

Studies on infants, preschoolers, and school children report a remarkable consistency in their findings. With a few exceptions, most such studies show that IDA, on average, is associated with poor performance in infant developmental scales, IQ and learning tasks in preschool children, and educational achievement among school-age children.

Infancy and Early Childhood (0–24 months)

An illustration of the consistency of the findings across different studies is found in the case of infants and young children with moderate IDA (Hb 100 g/liter). Without exceptions, the differences in the scores [mental development index (MDI)] on the Bayley scales of mental development among

[2]The Raven Progressive Matrices is an alleged cultural-free test that assesses nonverbal intelligence and has been widely used in clinical as well as in developmental research.

infants with sufficient iron stores and with moderate IDA have ranged from one-half to one and one-half a standard deviation. This developmental test score pattern has been reported in studies of infants in industrialized (e.g. United States, Great Britain) and developing countries (e.g. Guatemala, Thailand, Indonesia) (12, 21, 22, 27, 32, 41, 42). Few areas in developmental pediatrics observe such distinct patterns. For example, the well-researched area of behavioral alterations and elevated blood lead levels has observed neither the consistency nor the strength of the associations that characterize IDA test score patterns (7, 25).

There are some disagreements between findings in the case of milder IDA. Not all studies have reported a comparatively poor performance of infants with mild IDA (22). Those disagreements can be explained by the positive covariation that has been observed between Hb level and mental scores on the Bayley Scale (1, 22, 41). In some instances the effect of IDA on the MDI might remain undetected because of a weakness in the research design that did not include a sample with enough subjects. However, in a recent study the MDIs of infants with mild and moderate degrees of anemia did not differ from each other, and both scores were lower than those of infants without ID (14).

Within the range of IDA that has been studied, duration and not severity per se may account for a low level of test performance. As these two properties of IDA are confounded with each other, there is a risk of attributing the effect to one (e.g. severity) and not to the other (e.g. duration). A valid discrimination of effects between such attributes could only be achieved with accurate quantitative data on the course of the deficiency.

The large difference (e.g. one-half to one standard deviation) between the developmental test performance of infants with and without IDA should *not* be interpreted as an indication of a severe developmental delay in the infant with iDA. In most instances, the mean MDI of infants with moderate IDA has been within the range of the performance expected in healthy, average infants in the United States. For instance, the mean MDI of infants with a Hb 105 g/liter was 94.6 in Costa Rica (22) as compared to the average MDI of 100 for the standardized population of the Bayley Scale (standard deviation = 16). Briefly, a large and statistically significant difference between the MDI of infants with IDA and infants with replete iron stores is not necessarily a sign that the IDA infants are developmentally delayed as compared to the reference population (11).

It is still not possible to draw conclusive inferences regarding the association between ID without anemia and infant development even though most studies that have assessed such a theoretically reasonable association have found no statistical evidence to support it. A low-level association might remain undetected because of a lack of power in the research designs. The sample

size that may be required is possibly larger than that previously used. Some support for the argument that even in the absence of anemia ID could affect test performance is found in the improvement observed in the MDI of nonanemic iron-deficient infants following iron therapy (26). Moreover, a study in Thailand with school children that included, up to the time of its publication, the largest sample ever used with any age group did find a statistical association between ID without anemia and poor performance in school achievement tests (32).

Infants with IDA are also delayed in motor maturation as reflected by comparatively poorer scores on the Bayley Scale of Motor Development (14, 22, 41); few studies (42) that test this relationship failed to see the developmental delay observed in most other studies (14, 22, 41). However, in contrast to the positive association observed between severity of anemia and magnitude of delay in the MDI, those studies that reported an association between moderate and mild IDA and poor motor development scores have failed to see a correspondence between level of motor delays and the severity of the anemia.

Whether or not IDA is associated with delays in the timetable of critical motor milestones such as creeping, standing, or walking is not yet known. In one study, IDA in infancy was associated with delays in motor balance and coordination four years later (23).

Of particular importance to our present concern is that infants with IDA also show behaviors characterized by a disengagement from the task at hand during developmental testing. In agreement with what is observed in clinical exams, IDA infants have been described as unhappy, tense, fearful, or withdrawn as well as less responsive to testers and less goal directed (24). Briefly, they seem to be less active than expected for their age. Infants that show some of these behaviors are generally those that obtain the poorer scores on the developmental scales (24). Following therapy, however, the atypical affective state changed and the infants' responsiveness to the social environment became equivalent to that of iron-replete infants (26, 30). This change has been observed in a few instances a week or two after the iron intervention (26).

Preschool and School Children (≥24 months)

While maintaining socioeconomic status (SES) constant, studies show that the performance of IDA children from the ages of two to about five years has been poorer than that of iron-sufficient children in tests of intelligence and of particular cognitive processes (e.g. discrimination learning) (34, 39). For instance, the number of trials it takes a child with IDA to learn how to discriminate between almost but not completely identical visual stimuli on the

basis of particular cues is larger than among controls (39). One explanation for these differences is a diminished ability to attend selectively to available environmental information. Another explanation that does not exclude the attention hypothesis is that children with IDA maintain a dysphoric state and have reduced motivation that interferes with test performance. Observations of test behavior similar to those that have been made among infants are needed, particularly because, as previously noted, research with infants has shown changes in affect after iron therapy.

With exceptions (32), IDA among school children ($\geq$ 6 yr old) has been associated with poor performance on intelligence tests such as the WISC. The magnitude of the IQ differences between subjects with IDA and subjects that are iron replete has been about one-half of a standard deviation.[3] IDA has also been associated with comparatively poor performance on tests of specific cognitive processes such as short-term memory and attention (37, 38) and with comparatively low scores in school achievement measures (32, 38). For example, in rural Thailand the scores in a school language test of 8- to 11-yr-old iron-deficient children with and without anemia lagged behind that of iron-sufficient children (32).

Iron deficiency anemia among infants also predicts performance in cognitive tests at a later developmental period. In Costa Rica 5-yr-old children with histories of chronic and moderately severe IDA (Hb 100 g/liter) during early childhood scored lower in a wide range of tests of cognition (e.g. quantitative concepts, visual matching, nonverbal IQ) than a group without IDA in their nutritional history (23). At age five there was no evidence of IDA in any of the groups of children that were compared. Similar differences in test performance between the previously anemic and controls were observed in tests of fine and gross motor proficiency.

The cognitive test performance of the Costa Rican children with a history of mild IDA in infancy did not differ from that of well-nourished controls. An exception were children, mildly anemic in infancy (Hb 101 to 110 g/liter), who had not corrected their iron deficiency following 3 months of iron therapy. In follow-up testing, their performance did not differ from that of the moderately anemic children; however, it was poorer than that of the controls (23).

In sum, despite the differences in the nature of the psychological tests that were administered to infants with IDA and older children, there is strong agreement in the findings across age groups. Independent of age, the subjects with IDA perform, on average, less well than those whose iron stores are

[3]Most intelligence scales such as the Wechsler Scale for Children have a mean of 100 with a deviation of 16 IQ points and a standard error of 6 points (43).

replete, in so-called mental tests. Among infants up to 2 years of age, the poor developmental test performance is more likely to be observed among those whose Hb 105 g/liter. Among preschool and school age children, the relationship between psychological test performance and severity of anemia has not been explored sufficiently well to warrant an inference.

IRON DEFICIENCY AS A CAUSE OF ALTERATIONS IN COGNITION

Association, time order, and direction of effects, are the three main criteria for establishing causality (20, 40). Among these, the only one that must be met through appropriate experimental design is the direction of effects. Unlike any other design, double-blind, randomized clinical trials can determine whether a change in outcome is a consequence of a change in an antecedent variable. Accordingly, the present focus is on data from studies that meet the requirements for causal inference because of their research format. Only those studies that assigned subjects to iron and placebo conditions within iron status class are included. Data from quasi-experimental studies with designs that provided iron treatment for subjects that differed in iron status are included as backup.

Infancy and Early Childhood (0–24 months)

The trials that tested the developmental effects of IDA during the first two years of life are classified into two categories according to the interim time between the pre- and post-treatment evaluation. One group includes trials that assessed effects of either intramuscular or oral iron interventions for 7 to 10 days (21, 22, 26, 27, 41, 42). As noted, the studies in this first group intended to test the hypothesis that ID results in the cerebral depletion of cellular iron, which, in turn, affects cognition. The other set of published studies assessed the same effects after 8 to 16 weeks of oral iron therapy, but did not discriminate among mechanisms (1, 14). The hemoglobin of infants originally diagnosed with IDA generally falls within the normal limits after 8 weeks of iron intervention at a dosage that accounts for age and body weight. Therapeutic trials to correct IDA generally include 3 to 6 mg of elemental iron per kilogram of body weight daily.

Among infants with IDA, the effects on the BSMMD, observed 7 to 10 days after the administration of oral or intramuscular iron, have not differed from those observed after the administration of a placebo. This statement is valid for most studies. One exception is a study conducted in the United States (26). Seven days after the intramuscular administration of iron calculated to provide sufficient iron to raise the Hb to 120 g/liter, infants with IDA experienced a significant improvement (14 MDI points) in their performance

on the Bayley Scale of Mental Development. Conversely, the upward change (6 points) of the subjects exposed to placebo was not statistically significant. However, the difference between the two groups in the size of the MDI changes (8 points) was also not statistically significant.

In a trial that excluded a placebo condition, large developmental improvement was observed 11 days after the administration of intramuscular iron (48). The MDI increase among nonanemic iron-deficient infants was 22 points, while the change in the iron-depleted and iron-sufficient infants did not exceed 6 MDI points.

Two double-blind, randomized clinical trials that tested the long-term developmental effects of iron therapy on infants with IDA found evidence consistent with a causal hypothesis (1, 14). In the most recent study (14), 12- to 18-month-old infants with IDA who were exposed to a 4-month iron oral intervention (3 mg per day of elemental iron per kilogram of body weight) had, on average, a 20-point incremental change in their Bayley MDI from a pre- to a post-treatment evaluation. Conversely, the MDI increment in the infants with IDA who received placebo was negligible.

The iron-dependent change in the psychomotor development index (PDI) (24 points) was even larger than the change in the MDI. In addition, the MDI and PDI responses of the iron-sufficient and nonanemic iron-deficient cases to the iron and placebo interventions were inconsequential (14).

A previous study that used the Denver Developmental Screening Test[4] included an interim time of 8 to 9 weeks from the pre- to the post-treatment developmental evaluation (1). IDA infants with a modest Hb response to the iron therapy (20 mg per day of ferrous sulfate) showed a nonsignificant developmental change on the Denver Scale. Significant changes in test performance were observed among those whose Hb response to the intervention was equal or larger than 20 g/liter. The probabilities of improvement on the developmental scale were also positively related to the success of the treatment.

The differences in the developmental response of the infants with IDA in the two studies (1, 14) reviewed above are likely to depend, in part, on how successful a recovery followed the interventions. As noted, iron therapy lasted four months in one study (14), and all children who received this treatment fully recovered from the IDA. In the previous study, the treatment was restricted to two months and IDA was not fully reversed in all cases.

These two double-blind, randomized, clinical trials point to a causal relation between IDA and developmental behavioral alterations in infancy. They also

[4]The Denver Developmental Screening Test was devised to identify infants and young children at risk in four main areas: gross motor, language, fine motor adaptive, and personal social. It does not attempt to characterize mental and motor development.

show that, at least within the age range and degree of severity in the IDA that were studied, these alterations are reversed following the repletion of iron stores.

The findings reviewed above are at odds with those of most studies that tested the effects of oral and intramuscular iron over 7 to 14 days. Briefly, while the 2 clinical trials showed effects 2 to 4 months after baseline, 4 of the 5 trials that tested for effects over 7 to 14 days did not observe any such changes. This discrepancy suggests that, among infants and young children with IDA up to about 24 months, a sudden increase in cerebral iron following iron intervention does not produce a similar upward change in performance in developmental tests.

A pattern that emerges from the findings of quasi-experimental studies is that in some cases iron therapy for 12 weeks was not sufficient to improve the MDI of IDA infants although it did improve the PDI (1, 22, 41). This pattern was particularly clear among cases of moderate anemia (Hb $\leq$ 100 g/liter) that failed to show full reversal of the nutrient deficiency, and it coincides with a part of the findings of the Denver Developmental Screening Test previously reviewed.

Preschool and School-Age Children ($\geq$ 24 months)

Recently published studies on the performance of IDA preschool and school children in cognitive and school achievement tests have used double-blind testing and random assignment to either iron therapy or placebo condition within iron class (32, 34, 37–39). Accordingly, there is a data base that allows for testing causality.

Preschool children with IDA that were exposed to iron therapy have shown improvements in performance in some cognitive tests that were not observed among those that received placebo. Illustrative are studies in India and Indonesia where the interim time between the first and second test was about 8 weeks. In India, the pre- to post-treatment changes in the Verbal and Performance IQ (WISC) of IDA (Hb 105 g/liter) subjects that received iron were greater than 10 points respectively (37), while those of subjects on placebo was less than 6 points. These differences between groups were particularly striking in the Performance Scale of the WISC. The IQ of those on placebo improved from 98 to 104, while the IQ of those on iron changed from 100 to 117. This 17-point change in IQ is reminiscent of the 20-point change in MDI observed in IDA infants treated with iron.

In the study of preschool children in Indonesia (39), the size of the improvement in a battery of learning tests was not as striking as that observed in India (35). However, the differential change in 2 of the 3 cognitive tasks (i.e. discriminant and oddity learning) that were administered among IDA (Hb 110 g/liter) preschoolers with and without exposure to a dose-appropriate

8-week iron intervention was consonant with the causal hypothesis. For instance, the size of the decrement in the number of errors in discriminant learning tasks among the IDA subjects treated with iron was larger than that occurring in the placebo group. However, the changes in performance were not as large as had been expected. This finding may also be associated with the duration of the intervention (8 weeks) and with its moderate success in replenishing iron stores.

The results of 4 of the 5 clinical trials on school children are similar to those observed among preschoolers (32, 37, 38). School children with IDA who were exposed to a dose-appropriate iron intervention showed a significant improvement in their performance on tests of particular cognitive processes (e.g. attention, visual-perceptual organization, short-term recall) that was not observed among IDA children of the same age who received a placebo. The effects of IDA are obviously relevant to educational concerns and policy.

The battery of psychological tests used in 2 of the 5 studies with school children included school achievement measures (32, 38). The respective results, however, are in conflict. In one of these trials (38) 9- to 11-year-old Javanese children with IDA in grades 3 to 5 performed less well in standardized educational achievement tests than did iron-replete children. After 12 weeks of iron treatment the anemic children showed a marked improvement in their test scores, whereas the test performance of the anemic children that received a placebo remained stable from the first to the second testing. Note that the post-treatment score of the IDA children treated with iron still lagged behind that of the children who were replete at the beginning of the study.

In contrast to the results in Java, a study in Thailand failed to show the expected improvement in educational test scores among IDA school children treated with iron (32). The Thai study included 16 schools and a total of 2,268 children aged 9 to 11. These children were randomly assigned to an iron and placebo intervention for 14 weeks. After the code for randomization was broken, 1,358 children met 1 of 3 iron status criteria (i.e. IDA was defined by a Hb 120 g/liter plus two of the three following criteria: serum ferritin 10 μ/liter, transferrin saturation 16%, and free erythrocyte protoporphyrin 700 μg/liter RBC. Iron depleted was defined by the same criteria except for a Hb ≥ 120 g/liter). At base line the IQ (Raven Progressive Matrices) and the mean scores in a Thai language test of the children with IDA and ID were significantly lower than those of the iron-replete group. However, these differences remained unchanged following the experimental intervention.

In sum, the results from clinical trials on preschool and school-age children with IDA show a distinct pattern. In general, among IDA subjects, dose-appropriate iron interventions that lasted for two months or more resulted in major improvements in IQ or in one or more tests that tapped particular

cognitive processes such as attention. In contrast, the changes in test performance observed among IDA subjects that received placebo were inconsequential. In conclusion, iron deficiency anemia causes an alteration in cognitive function among preschool and school age children that is reversible following the repletion of iron stores.

ON THE NATURE OF THE EFFECT

Having established that IDA increases the probabilities of a deviation on the developmental trajectory of a child, I now turn to the question, What is the specific nature of the psychological effect? This discussion is presented with the admonition that on this particular issue the evidence is insufficient to draw conclusions. At best, only inferences are warranted.

Ideally this discussion should begin with a definition of the locus of the biological system that is altered by iron deficiency which results in the behavioral changes that have been observed among children with IDA. However, this ideal must defer to a future date because, in my view, the information currently available is insufficient to define the genesis of the behavioral problem. Despite claims to the contrary (46, 47, 50), we are not yet able to determine whether the underlying problem is a reduction of nonheme iron in the brain or other systemic changes in the organism associated with the reduction in the transport of oxygen. While there is no reason to assume that these two explanations are mutually exclusive, the arguments that address causality focus almost exclusively on the role of iron in the brain (8, 31, 33). Moreover, the compensatory mechanisms activated by the organism in the presence of mild to moderate anemia suggest that the root of the problem is not found in the reduction of hemoglobin (16).

The data and arguments in favor of a neurochemical explanation are found in recent publications (8, 31, 49) and are the subjects of controversy (4, 13, 18, 19, 46, 48–50). This review focuses on an analysis of the psychological test data, particularly on some of the conclusions presented in the previous sections: (*a*) the consistently poor psychological test performance of IDA subjects across ages, (*b*) behavioral descriptions on affect and motivation, and (*c*) magnitude of the effects in test performance.

As previously discussed, numerous psychological tests have discriminated between infants, preschoolers, and school-age children with and without IDA. How do we explain the striking agreement of the results obtained if, as already noted, the tests that have been administered to young and older children do not tap the same psychological constructs? In my view, the following considerations regarding the constructs behind the tests are useful in discussing this issue. One possibility is that IDA has a uniform effect across age groups

on a particular cognitive function that is tapped by all tests that have been administered across age groups.

If this were the case then the similarity in the findings among infants and older children is not surprising. A second possibility is that IDA affects multiple functions independent of age and that the different tests that have been used tapped at least some of those multiple functions. Finally, the possibility exists that the functional effects in infants and young children are different from those observed among older preschoolers and school children and that the tests administered at these respective ages (e.g. BSMMD up to 24 months) are sensitive to those particular age effects. The following discussion focuses on these three possibilities.

The interpretation that the tests tap the same cognitive construct and function must be rejected on theoretical and statistical grounds. Analytical comparisons of the objectives of the tests that have been used (e.g. Bayley Scales, Oddity Learning, and Raven Progressive Matrices) point to a wide variability in the constructs they tap. Moreover, psychometric data uncover discriminant functions. For example, statistics on predictive validity show either a zero or a low-level correlation between the MDI of the Bayley Scale (used in the infancy studies) administered at 12 months of age and an IQ obtained at 5 years (11, 29). These correlational data do not address the reliability or the validity of either test, but they do show a lack of convergence between tests.

To test the possibility that a wide spectrum of psychological functions are affected by IDA or that the functions that are affected differ by age would have required systematic, focal assessments of different functions and of different age groups. What is available is far removed from meeting these two criteria; there are few instances where attempts were made to assess particular functions (e.g. attention) that were assumed to be affected by iron deficiency among particular age groups (23, 39). There are also posthoc data-driven analyses of the items in the BSMMD that were most likely to discriminate between infants with IDA and controls. In any event, these available data show that with the possible exceptions of attentional processes (across ages) and verbal items of the BSMMD (in infancy) that seem to be sensitive to IDA, there are no consistent data that point to effects on multiple distinct functions.

When the focus of concern moves away from cognitive function, the picture is clearer. The pattern that emerges from the existing data with infants and older children is that IDA has an effect on affect and motivation that interferes with attentiveness (time on task). As noted, studies have shown that during testing infants with IDA are unhappy, tense, fearful, or withdrawn (20, 24), and that therapy reverses the dysphoric behavior. Studies among older children, on the other hand, have reported alterations in attention and in the reception of environmental information. Conjointly, these observations may

explain the poor performance on observed discriminant and oddity learning tasks among preschoolers. Briefly, it does seem likely that a relatively narrow effect on affect and motivation and reduction of motor activity precludes good test performance among infants and preschool and school-age children. Thus, there may not be a direct effect on cognition but an indirect effect through affective states and motivation.

Changes in test performance of about one standard deviation over a period of 2 to 4 months can also be explained by a narrow effect on affect and motivation. Decrements in tension and fear, with increments in sociability and positive affect, lead to increased engagement with tasks and therefore to better test performance. On the other hand, the large increments in test scores clash with the assumption of multiple functional effects, as one would expect that rates of recovery in different cognitive process would vary widely.

Narrow effects on affect and motivation could have broad developmental implications. First, these effects would explain the poor performance of infants in motor and mental development scales, and of preschool and school age children in IQ tests, learning tasks, or school performance. Accordingly, the comparatively poor scores in such a large array of psychological and educational tasks would have no relation to the particular psychological constructs that are purported to be assessed by the tests that have been used. The poor scores would be the result of an organismic state that is largely incompatible with doing well on a test—any test.

A dominant effect on affect and motivation is not likely to involve the neural and chemical basis for complex cognitive processes. In fact, the effect could be a restricted alteration in the first step of the process through which the organism changes signals into responses. In particular, I am referring to alterations in arousal (i.e. alerting effect of sensory signals) and activation (i.e. motor disposition to respond) that are critical and distinct components of attention (36). Decrements in these two processes in infants and children would have the distinct effect of altering the responses to different kinds of tests and would, therefore, explain why the test performance of IDA is consistent across age groups.

In conclusion, iron deficiency anemia is a risk factor that increases the probabilities of deviation in the development of infants and children from a normal developmental trajectory. At this time, however, this conclusion cannot be securely tied to a particular set of mechanisms related to the role of cerebral iron or to possible systemic changes associated to anemia.

In particular, neither the data on developmental test performance nor the existing information on the consequences of altered dopamine neurotransmission are sufficiently detailed to validate the hypothesis that the decrements in iron-dependent dopamine D2 receptors in the cortex explain the observed behavioral alterations associated with iron deficiency anemia. In my opinion,

the most suggestive data from studies in humans that could be tentatively used in favor of such a mechanism lie in the area of motor activity. As previously suggested in this review, perhaps the clearest evidence of a causal effect of iron deficiency on behavior is in the area of psychomotor development. On the one hand, while the particular motor functions altered by iron deficiency are not yet clearly defined, we now know that infants and young children with IDA score poorly in motor development tests and that this performance has been shown to improve significantly with iron therapeutic trials in experimental and quasi-experimental studies. In addition, it has been observed that infants with IDA display less motor activity and maintain closer physical proximity to their mothers than infants with replete iron stores (20). This type of motor display has also been shown in laboratory studies of experimentally induced iron deficiency among rodents (43, 48, 49). On the other hand, we also know that dopamine antagonists produce states of hypo-motility and reduced ambulatory activity and that these effects are dose related. However, note that other drugs such as GABA agonists also produce significant decrements in motor activity (28).

The gaps in knowledge, however, should not affect program implementation. The data presented represent a strong justification for interventions to prevent and remedy iron deficiency wherever needed.

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