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Motor Activity and intra-individual variability according to sleep–wake states in preschool-aged children with iron-deficiency anemia in infancy ☆

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ABSTRACT

Background: A chronic or acute insult may affect the regulatory processes that guide motor and behavioral performance, leading to increased intra-individual variability (IIV). Increased variability is often interpreted as an indication of regulatory dysfunction. Iron plays an important role in the regulatory processes of the nervous system and affects motor activity. To our knowledge, no study has examined the long-lasting patterns and IIV of motor activity following iron-deficiency anemia in human infants.
Aims: This study compared 48-h motor activity and variability in preschool-aged children with or without iron-deficiency anemia (IDA) in infancy.
Methods: Motor activity was recorded through actigraphs during two week-days in 47 4-year-old Chilean children (23 former IDA and 24 non-anemic in infancy). All were given oral iron as infants. Sleep–wake states were identified by means of automated software. The frequency of movement units per minute was determined for each waking/sleep state during the individual day and night periods; data were examined in blocks of 15 min. Analyses of mean frequency and duration and intra-individual variability were conducted using multivariate mixed models.
Results: For daytime sleep, former IDA children were more active without a difference in the total duration. They also spent less time awake throughout the individual day period. Motor activity intra-individual variability was higher in former IDA children.
Conclusions: The findings suggest that IDA in infancy sets the stage for long lasting dysfunction in the neural processes regulating sleep–wake states and spontaneous motor activity patterns.
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1. Introduction

Being physically active is a critical component of proper development. Motor activity, especially in the first years of life, has a positive impact on child health and motor, cognitive, and socio-emotional well-being [1–6]. Iron deficiency anemia (IDA) in infancy, a common nutrient disorder worldwide, is associated with altered motor activity in animal models and humans [7–9]. However, long-lasting effects of early IDA on motor activity patterns have not been examined in the human. The effect of this nutritional insult on intra-individual variability in motor activity, a marker of the stability of regulatory processes, has also not been investigated.

1.1. Iron deficiency and motor activity

Changes in motor activity associated with early IDA have been reported in animal models. Studies in rodent models have reported a wide range of modifications ranging from reduced locomotor activity during the period of IDA [10] to altered circadian patterns of motor activity [11,12]. Two studies that systematically varied the timing of IDA during early development found that IDA rat pups showed decreased activity [13] and moved less in a home-orienting task [12]. In the primate, prenatally iron-deprived infant monkeys showed reduced motor activity and postnatally iron-deprived monkeys slept more at night over a 48-h period, compared to controls [9]. In addition, a small pilot project involving juvenile monkeys reported dramatic decreases in running and playing, even in those animals with mild iron deficiency anemia [14].

In the adult human, maximal physical performance, submaximal endurance, and work productivity have been shown to be reduced in individuals with IDA and, in some cases, iron deficiency (ID) without anemia [15–19]. Treatment with iron improved physical performance and endurance [20]. Only a few studies have reported motor activity

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in human infants and children while IDA or after treatment. In a study of play behavior and mother–infant interaction, Lozoff et al. (1998) found lower activity in IDA infants using crude measures (crossing gridlines in a play room, moving beyond arm's length from the mother, etc.) [21]. In a study of 12- to 18-month-old undernourished infants with IDA, Harahap et al. (2000) found lower motor test scores and motor activity scores compared to controls before iron therapy. Following iron treatment, the activity of IDA infants increased to a larger extent than controls [22]. Similar results of lower activity in IDA children were found in Zanzibari toddlers as they initiated independent walking [23]. In a study performed in Chile using actigraph recordings in the home, we found overall *increased* activity during the day and night, in both waking and sleep states, in 6-month-old infants while IDA [7,24]. In contrast, they showed *decreased* motor activity in a laboratory (i.e., unfamiliar) setting after iron treatment (at 12 and 18 months). The few published studies of concurrent iron deficiency and motor activity in school-aged children report lower activity [25].

1.2. Motor activity and intra-individual variability

Activity in young children is typically intermittent and includes frequent transitions across different magnitudes of activity [26]. This pattern generates intra-individual variability (IIV). A chronic or acute insult may affect the regulatory processes that guide motor and behavioral performance, leading to altered IIV patterns and, in particular, increased IIV. Several studies show increased IIV in the motor behaviors of aging populations [27] and populations with diseases or disorders, such as stroke [28], post-traumatic brain injury [29], or ADHD in children [30]. For instance, children with ADHD show more IIV in motor timing tasks compared to typically developing peers. In fact, IIV was a better indicator of ADHD than performance alone [30].

In terms of development, IIV shows a U-shaped pattern from birth to adulthood [31,32]. In contrast, magnitude of motor activity shows the opposite, that is, an inverted U-shaped pattern [2]. Such an inverse relationship is unlikely to be explained by a ceiling effect, since physical activity levels can be greatly increased with purposeful exercise practice even at young ages [33]. Typically, children's motor activity increases and IIV decreases with advancing age up to approximately 7–9 years of age [34]. Given the role of iron in myelination, neurometabolism, and neurotransmitter function [35], iron deficiency in infancy might contribute to increased IIV in motor activity. To our knowledge, no study to date has considered this question.

The purpose of the present study was to assess the magnitude of spontaneous motor activity and IIV for 48 continuous hours in the home among preschool-aged children who did or did not experience IDA in infancy. On the basis of the revised literature, we hypothesized that former IDA children would demonstrate lower levels of motor activity but higher levels of IIV compared to control children.

2. Methods

2.1. Participants

This study of motor activity was conducted in conjunction with the neurophysiological components [21] of a larger study in Chile on the long-term behavioral and neuromaturational effects of IDA in infancy. Activity could be measured in only a subset of the children at the preschool follow-up, as funding limitations precluded activity monitoring in all. Nonetheless, we considered that studying spontaneous motor activity for 48 continuous hours with more advanced techniques promised to provide new information about the long-lasting effects of IDA in infancy. Detailed descriptions of the population and other findings during infancy and the preschool period have been published elsewhere [7,24,36–38].

Participants in this study had been born healthy, at term, weighing ≥3.0 kg and were free of acute or chronic health problems as infants (for further details of inclusion criteria, see [35,36]). Based on a venous blood specimen at 6, 12, or 18 months, IDA and control children were identified. Anemia was defined as a low hemoglobin for age (a venous hemoglobin ≤100 g/L at 6 months or <110 g/L at 12 and 18 months [39]). Iron deficiency was defined as two or more iron measures in the deficient range (mean cell volume <70 fl [40], erythrocyte protoporphyrin ≥1.77 μmol/L [100 μg/dL] red blood cells [41], serum ferritin <12 μg/L [41]), or an increase in hemoglobin ≥10 g/L after 6 months of iron therapy [40]). IDA was defined as anemia plus iron deficiency. Seven infants were identified as IDA at 6 months, 11 at 12 months, and 5 at 18 months. The control group consisted of randomly chosen children who were clearly nonanemic (venous Hb ≥ 115 g/L). Six-month-old infants were treated orally for one year with 15 mg/day of elemental iron as oral ferrous sulphate (Fer-in-Sol®). A venipuncture was repeated at 12 months to determine response to therapy, using hemoglobin level and iron status measures. A finger-stick hemoglobin level was obtained at 18 months to monitor maintenance of response [see refs. 36,37 for full details]. Infants identified at 12 or 18 months were treated with oral iron (30 mg/day) for a minimum of 6 months. Finger-stick hemoglobin levels were also obtained after treatment to monitor maintenance of response. Given that IDA in infancy was very common in the population at the time, infants from the control group underwent the same iron treatment in order to assure that they did not become anemic with advancing age. Neither parents nor project personnel were informed of an infant's hematologic status.

All aspects of the study were explained to parents of qualifying children, and signed informed consent was obtained. The research protocol was approved by the Institutional Review Boards of the University of Michigan Medical Center, Ann Arbor, of INTA, University of Chile, Santiago, and of the Office of Protection from Research Risks, NIH.

Of the available preschool-aged children who had been part of the infant studies (former IDA and control groups), we conducted activity monitoring in those who were under 5 years of age, depending on availability of a device. Data were collected for 23 children who had IDA at 6, 12, or 18 months of age and 24 children who had been non-anemic throughout infancy. No child had IDA when blood was collected at 5 ½ years (blood was not obtained at earlier ages in the preschool follow-up). The children were well-nourished with growth at the U.S. 60–70th percentile, on average, upon entry into the study and at the childhood testing time. Their overall development was comparable to that of U.S. infants and children as assessed by the Bayley Scale of Infant Development II [42].

2.2. Procedures

As part of the preschool-age follow-up, children were scheduled for an overnight polysomnographic sleep recording [38]. Upon waking in the morning, an actigraph (Ambulatory Monitoring, Inc.) was attached to the child's right ankle with a Velcro band for 2 consecutive days. These actigraphs are computerized activity monitors with a piezoelectric sensor sensitive to accelerations above .01 g per radians/second and an internal memory. The actigraph counted each such acceleration, digitizing and storing in memory the total number of accelerations–decelerations (movement units) per 2-s interval. The weight and dimensions of this device are minimal (56.7 g, 4.45 × 3.3 × .97 cm) and do not interfere with children' actions.

The subset of children under 5 years of age who received activity monitoring was determined solely by the availability of our limited number of actigraphs. Further, a few actigraphic recordings were technically inadequate. Satisfactory recordings at preschool age were obtained for 23 IDA and 24 controls. There were no differences between children who did or did not have activity data with respect to factors including gender, birth weight, growth, and family background. The exception was the home environment (HOME): children with activity data had more supportive home environments in infancy than those who participated in the preschool follow-up but had no activity data.

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