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Original Article

Sleep and motor sequence learning consolidation in former iron deficient anemic adolescents

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ABSTRACT

Background: Iron deficiency is the most prevalent micronutrient deficiency worldwide. There is evidence that iron deficiency produces alterations in the developing brain, eventually leading to long-lasting effects on various cognitive functions.
Methods: Here, we investigated motor learning and its consolidation after sleep in adolescents who sustained iron deficiency anemia (IDA) in infancy, compared to healthy controls, in the context of a long-term follow-up Chilean research project. Fifty-three adolescents who formerly had iron deficiency anemia as infants and 40 control adolescents practiced a sequential motor finger tapping task, before and after a night of sleep. Performance was measured at the end of learning, 30 min later (boost effect), and the next morning.
Results: Revealed slower learning in subjects with infant iron deficiency anemia than control subjects, followed by a proportionally similar performance boost at 30 min. Performance remained stable overnight in healthy controls but further improved in infant IDA adolescents, suggesting a beneficial effect of post-training sleep on the consolidation of incompletely learned motor skills. In particular, overnight gains in performance were observed in female, but not male infant iron deficiency anemic subjects, suggesting a gender effect.
Conclusions: Our results indicate long-lasting motor learning deficits in infant IDA adolescents and provide support to the hypothesis that post-training sleep might, to some extent, compensate for hampered motor learning during wakefulness.

1. Introduction

Iron deficiency anemia (IDA) affects mainly infants, pregnant women, and older adults in developing countries, but remains present in developed countries with a prevalence range of 1.5–2.9% [1]. Animal models show that even marginal IDA during early development can alter the expression of genes relevant for myelination and dopamine receptor subunits [2,3]. Iron deficiency is also related to metabolic and structural alterations in the hippocampus, (ie, impaired brain energy metabolism and altered neuronal dendritic structure and motility) [4,5]. There is also evidence that IDA in infancy exerts a significant, long-term impact on the brain and cognitive functions [6,7]. These findings are in-line with long-lasting effects of early IDA on myelination and modifications of prefrontal-striatal circuits where dopamine is the major neurotransmitter.

Interactions between D1 and D2 dopamine receptors are likely involved in the regulation of motor learning [8]. Few longitudinal studies have investigated the relationship between motor

Abbreviations: IDA, Iron deficiency anemia; FIDA, Formerly iron deficiency anemia; FTT, Finger tapping task.

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development and IDA in infancy. Children who experienced severe and chronic IDA during infancy scored lower on a test of motor proficiency at five years and during early adolescence [9]. Long-term effects of IDA on motor functions might stem from reduced dopamine levels in the basal ganglia and its connections. Consequently, it might also interfere with the acquisition of new motor skills through repeated practice [10]. In healthy adults, the learning of motor skills was extensively studied using the finger tapping task (FTT) [11], in which participants must reproduce as fast and accurately as possible a simple sequence of five finger movements. With the progression of motor sequence learning, gradual changes take place in a brain network, including the dorsolateral prefrontal cortex, the sensorimotor areas, the basal ganglia, and the cerebellum [12].

Sleep-dependent brain plasticity mechanisms are known to contribute to the development of neurobehavioral functions [13]. In this respect, post-training sleep can trigger a better stabilization and/or improvement in procedural motor learning performance, as compared to post-training wake periods [14–18], at least under certain conditions. For instance, sleep was found to benefit procedural motor learning only when it is at an intermediate, but not at saturation level at the end of the learning episode [17]. Accordingly, children with ADHD who exhibited a slower learning curve than controls benefited from post-training sleep to improve performance, whereas it remained stable in controls who reached asymptotic learning [19]. These results suggest that sleep might, to some extent, compensate for deficits or weaknesses in the initial learning acquisition stage.

Early IDA was shown to result in long-lasting effects on sleep features and the modulation of motor activity both during sleep and wakefulness [20,21]. To the best of our knowledge, it remains unknown whether motor skill learning abilities are altered in formerly iron deficient anemia in infancy (FIDA) teenagers, and if their consolidation can benefit from sleep. Additionally, gender differences have been reported in motor skill learning [22,23]. Therefore, we tested whether (a) motor skill learning was different between FIDA and matched control participants, (b) to what extent post-training sleep might compensate for possible motor learning differences, and (c) taking into account participants' gender.

2. Methods

2.1. Participants

A total of 93 adolescents who had neuro-functional assessments at 15–16 years were included in the present study. All adolescents are participants in an ongoing longitudinal cohort study about the sensory, motor, socio-emotional, cognitive, and neuro-functional effects of IDA in infancy. The study design and participant characteristics in infancy have been reported elsewhere [24]; only essential information is provided here. Healthy full-term Chilean infants with a birth weight $\geq$ 3 kg, without perinatal complications, and absence of acute or chronic illnesses, were included in the study. Iron status was assessed in all infants recruited at 6, 12 or 18 mo and screened for IDA. For each IDA infant, a children of the same age identified as non-anemic (venous Hb $\geq$ 115 g/L) was invited to join the study as part of the Control group. All participants were treated with oral iron for at least six months to reach normal Hb concentration. They underwent follow-up assessments during preschool and primary school and adolescence. Participants who developed neurological or hematological diseases were excluded from the follow-up study. At the time of this study, socio-economic and educational status was collected. All participants were healthy, without any iron deficiency and regularly attending school. Given that adolescents had to spend mornings in the laboratory to complete the neurocognitive tasks, they had to ask for school's permission. To avoid school absence as much as possible, we carried out post-sleep assessments after the first night.

Parents provided signed informed consent, and adolescents signed an informed assent. The original and follow-up protocols were approved and reviewed annually by the Institutional Review Boards of the Institute of Nutrition and Food Technology (INTA), University of Chile, and the University of Michigan, Ann Arbor, USA.

2.2. Questionnaires

Circadian typology and sleep habits for the last month were assessed using the Spanish version of the Morningness and Eveningness Questionnaire (MEQ) [25] and the Pediatric Sleep Questionnaire (PSQ) [26], respectively.

2.3. Sleep recordings

Adolescents underwent two overnight polysomnographic (PSG) recordings at the Sleep and Functional Neurobiology Laboratory, INTA, University of Chile. They arrived at the laboratory at 8:00 PM to familiarize themselves with the personnel and the laboratory setting. PSG recordings started approximately at their usual bedtime and continued until spontaneous awakening the next morning. Recordings were performed using a Cadwell Easy EEG II system (Cadwell Lab., Kennewick, WA, USA) following standard recommendations in a separate, quiet and comfortable room with controlled temperature, light, and humidity. The recording set-up included an electroencephalogram (F3, F4, C3, C4, O1, O2) with electrode placement according to the 10–20 system [27] referenced to the contralateral mastoid, left and right electrooculograms, a chin electromyogram, and an electrocardiogram. Sleep signals were sampled at 200 Hz and stored in European data format [28]. Electroencephalographic signals were acquired with a wide-band filter (0.10–35 Hz), 12 bit A/D precision.

Sleep stages were scored according to the standard American Academy of Sleep Medicine (AASM) criteria [29]. Reported PSG parameters are time in bed, sleep latency, total sleep period, total sleep time, sleep efficiency, rapid eye movement (REM) sleep latency, and the percentages of non-REM sleep (1, 2, and SWS) and REM sleep stages.

2.4. Experimental motor learning task

The FTT [11] was administered on day one, before setting-up for the PSG night. The experiment was programmed and conducted on a PC using Cogent 2000 and Cogent Graphics (http://www.vislab.ucl.ac.uk) software implemented in MATLAB 6.1 (Mathworks Inc., Sherbom, MA). Subjects were instructed to repeatedly reproduce as fast and accurately as possible a five-element sequence of four possible key presses on the keyboard using four fingers of the non-dominant hand (sequence [4-1-3-2-4] from the index [1] to little finger [4]). The sequence was displayed on the PC screen at all times during performance to minimize working memory demands. We used the non-dominant hand to avoid ceiling effects since motor dexterity is usually lower for the non-dominant than the dominant hand [30].

During learning Session 1, participants reproduced the 5-elements sequence during 12 blocks of 30 s each, interspersed with 30-second rest periods (blocks A1 to A12). At test Session 2, a possible boost effect (ie, transitory improvement) [11] on performance was tested 30 min after Session 1 with two additional blocks (B1 and:B2). The 30-min interval between Sessions 1 and 2 was filled with questionnaires. For retest Session 3 the next morning, overnight changes in performance and continued learning were

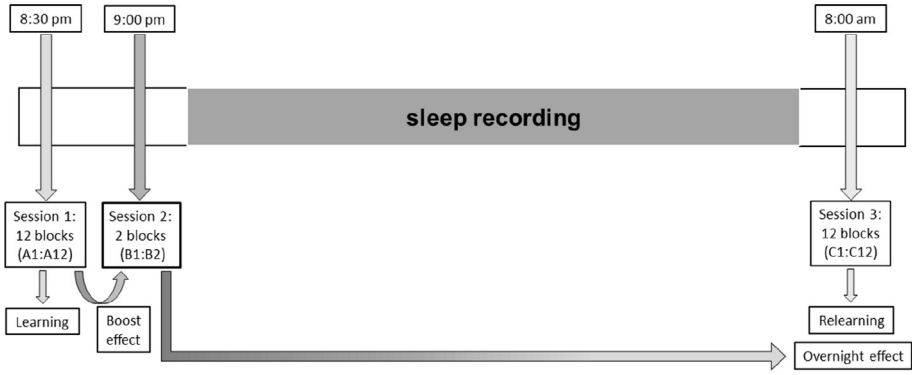

Fig. 1. Experimental procedure: Session 1 (Learning): 8:30 PM, 12 blocks (A1 to A12); Session 2: 30 min after Session 1, two blocks (B1 and B2); Session 3 (Relearning): 8:00 am, 12 blocks (C1 to C12); Boost effect: performance on Session 2 vs. Session 1; and Overnight effect: performance on Session 3 vs. Session 2.

tested again over 12 blocks (C1 to C12). Session 1 took place at 8:30 PM and Session 3 was administered at 8:00 am (Fig. 1).

Learning on Session 1 was assessed by computing the gradual progression of performance from blocks A2 to A12. The boost effect was assessed comparing performance averaged over the last two blocks of Session 1 (A11 and A12) vs. the two blocks of Session 2 (B1 and B2). The overnight effect was assessed comparing performance averaged over the two blocks of Session 2 (B1 and B2) vs. the first two blocks of Session 3 (C1 and C2). Finally, continued learning on Session 3 was assessed by computing the changes in performance from block C2 to C12. The first block (Session 1 and Session 3) was removed from the learning analyses to allow habituation to the task and to reach optimal accuracy [31]. Speed performance was computed as the number of correctly generated 5-element chunks per block. Accuracy performance was computed as the percentage of correctly generated five-element chunks out of the total number of five-element sets generated per block [11].

2.5. Data analysis

Data were analyzed using Statistica 7.0 (Stat Soft Inc, USA). Univariate analyses of variance (ANOVA) were calculated to compare sleep and circadian questionnaire data and PSG parameters, with conditions (FIDA vs. Control) and sex (male vs. female) as between-subject factors. Repeated measure ANOVAs were computed on performance measures (speed and accuracy) with block and session as within-subject factors and condition and sex as between-subject factors. Tukey post-hoc analyses were computed to decompose significant interaction effects.

3. Results

Fifty-three FIDA (63% male) and 40 Control (45% male) subjects completed the experimental protocol. Age did not statistically differ between condition (FIDA = 15.9+/−0.9 years; control = 16.1+/−1.1 years; p = 0.08) or gender (males = 16.0+/−0.9 years; females = 16.0+/−1.0 years; p = 0.61). Additionally, all between-group comparisons among background variables that could affect brain development were not significant (ie, birth weight, gestational age, mother's age at childbirth, maternal education, maternal IQ and socio-ecomomic status measured with the Graffar scale (Table 1).

Table 1
Background characteristics of Condition groups (mean ± standard deviation).

	FIDA n = 53	Control n = 40	*p*
Birthweight (kg)	3.2 ± 1.1	3.4 ± 0.6	NS
Gestational age (weeks)	39.2 ± 1.0	39.3 ± 1.1	NS
Mother's age at child's birth (y)	25.0 ± 5.4	26.3 ± 5.9	NS
Maternal education (y)	8.8 ± 3.0	9.9 ± 2.9	NS
Maternal IQ [a]	83.3 ± 10.4	86.8 ± 10.4	NS
Graffar scale at ten years old [b]	35.1 ± 6.4	33.1 ± 6.7	NS

Independent sample *t*-test.
FIDA: formerly iron deficient anemia in infancy; NS: non-significant.
[a] Wechsler Adult Intelligence Scale.
[b] [32].

3.1. Sleep

Univariate ANOVAs conducted on PSG sleep parameters (Table 2) disclosed a main condition effect on REM sleep latency, with FIDA participants having shorter REM latency than Controls (121.9+/−9.7 vs. 150.6+/−9.7 min). In respect to this, there was also a trend for a condition by sex interaction effect, with FIDA males exhibiting a shorter REM latency than Control males. A condition effect on time in bed was evident, with FIDA subjects showing a longer time in bed than Controls (485.5+/−12.7 vs. 459.6+/−13.6 min).

Regarding circadian typology and the sleep habits questionnaire, all effects were non-significant for the MEQ total score (mean score = 47.3+/−4.6; all ps > 0.34). For the PSQI, there was a main sex effect (p < 0.01), with a higher percentage of females reporting sleepiness than males over the last month (43.3% vs. 18.8%).

3.2. Motor learning

Fig. 2 illustrates the evolution of speed (top) and accuracy (bottom) performance over the learning Session 1 (A1 to A12), followed by the 30-minutes boost (B1, B2) Session 2 and the overnight retest and relearning Session 3 (C1, C12).

3.2.1. Learning (Session 1)

The repeated measure ANOVA conducted on speed performance over blocks A2 to A12 disclosed a main learning effect ($F(10,89) = 23.8$, $p < 0.0001$), with performance gradually improving from block A2 to A12 (6.7+/−0.5 vs. 10.8+/−6.2 sequences/block), and a main condition effect ($F(1,89) = 4.9$, $p < 0.03$), with overall higher performance for Control than for FIDA participants (10.7+/−0.7 vs. 8.3+/−0.7 sequences/block). The condition by learning interaction effect was also significant ($F(10,89) = 2.4$, $p < 0.008$). Planned comparisons computed between blocks (averaged) A2, A3 and A11, A12 show that although performance improved in both groups ($p < 0.001$), the performance gain was significantly higher in the Control than in the FIDA ($p < 0.035$) group (Fig. 3). Even though performance was ostensibly higher in male than female participants (10.4+/−0.7 vs. 8.6+/−0.8

Table 2
Polysomnographic parameters in FIDA vs. Control adolescents by Sex.

	FIDA males n = 40		FIDA females n = 13		Control males n = 18		Control females n = 22		Condition effect		Sex effect		Condition x Sex effect	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	F	p	F	p	F	p
Time in bed (min)	483.8	9.0	487.2	16.4	479.0	16.4	440.2	10.8	3.87	0.05	1.80	0.18	2.56	0.11
Sleep latency (min)	10.6	2.0	17.6	6.1	13.1	4.6	7.6	1.4	1.28	0.26	0.04	0.83	3.54	0.06 post-hoc p > 0.26
Total sleep period (min)	432.4	9.3	429.3	15.0	430.5	14.4	397.7	8.8	1.83	0.18	2.11	0.15	1.44	0.23
Total sleep time (min)	402.6	9.5	406.5	18.9	395.6	17.9	362.4	12.6	3.11	0.08	1.02	0.31	1.64	0.20
Sleep efficiency (%)	83.5	1.6	83.2	2.6	82.8	2.9	82.9	2.8	0.04	0.83	0.002	0.96	0.004	0.94
REM sleep latency (min)	111.1	7.0	132.8	17.3	165.3	16.5	135.9	16.7	4.31	0.04	0.07	0.78	3.42	0.07 post-hoc p < 0.05[a]
N1 (%)	7.5	0.8	8.1	1.6	6.3	1.4	6.7	1.0	1.15	0.28	0.21	0.64	0.01	0.92
N2 (%)	52.4	1.2	53.0	1.7	52.3	1.5	54.7	1.5	0.23	0.62	0.88	0.35	0.30	0.58
S3 (%)	23.4	0.8	22.8	1.6	26.9	1.8	22.9	1.2	1.79	0.18	3.06	0.08	1.74	0.19
REM sleep (%)	16.8	0.8	16.0	1.3	14.5	1.4	15.7	1.1	1.13	0.29	0.04	0.84	0.69	0.40

Univariate Analysis of Variance; Tukey's Post Hoc Test.
FIDA: formerly iron deficient anemia in infancy.
REM: rapid-eye-movement; N1, N2, and N3: stages 1, 2 and 3 of non-REM sleep.
[a] FIDA males vs. Control males.

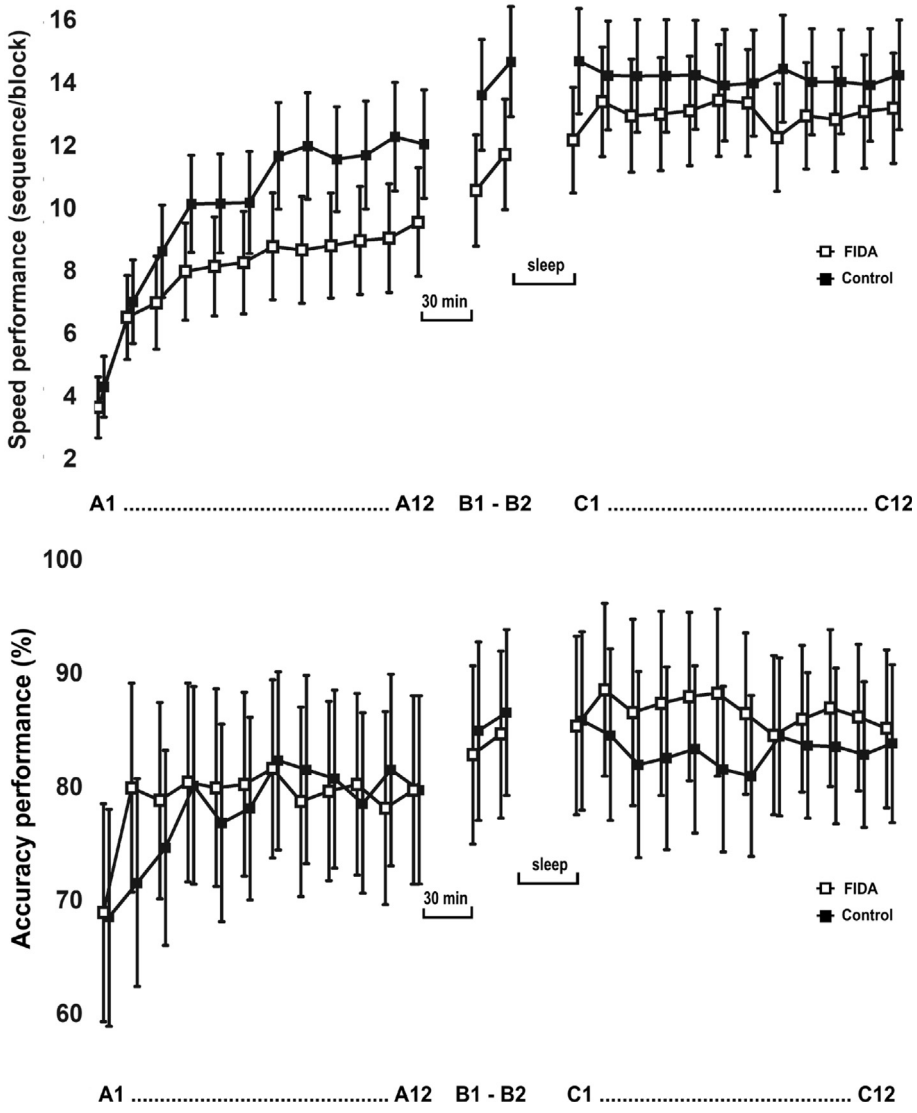

Fig. 2. Speed (top) and accuracy (bottom) performance: average number of correctly generated 5-element chunks per 30-sec block during Session 1 (blocks A1 to A12). Session 2 (blocks B1 to B2) and Session 3 (blocks C1 to C12) in formerly iron deficient anemic (FIDA) (open squares) and Control (filled squares) adolescents. Displayed data are mean performance values with 95% confidence interval.

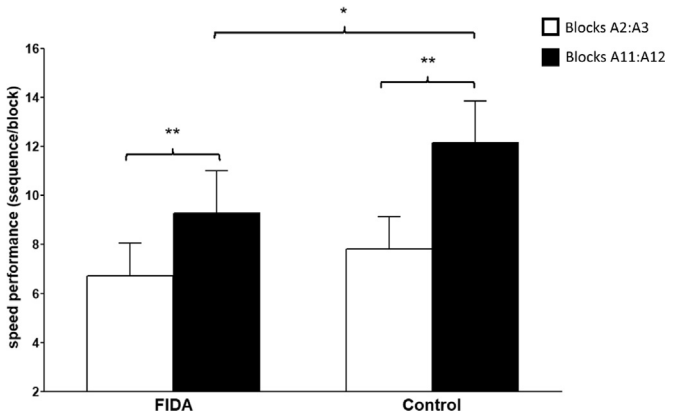

Fig. 3. Learning effect: summarized performance at the beginning (blocks A2 to A3 averaged, white bars) and end (blocks A11 and A12 averaged, black bars) of Session 1. Data are mean performance values with 95% confidence interval. Repeated measures ANOVAs. *p < 0.05 **p < 0.001; FIDA: formerly iron deficient anemia.

sequences/block), the sex effect was non-significant ($F(1,89) = 3.2$, $p = 0.08$). As well, the condition by learning by sex interaction effect was non-significant ($p > 0.48$). A similar repeated measure ANOVA conducted on accuracy performance over blocks A2 to A12 failed to disclose any significant effect (all ps > 0.08).

3.2.2. Boost effect (Session 2 vs. Session 1)

The repeated measure ANOVA conducted on speed performance (blocks averaged B1 and B2 vs. A11 and A12) disclosed a main session/boost effect ($F(1,89) = 35.4$, $p < 0.0001$), with higher performance in Session 2 than Session 1 (12.6+/−0.6 vs. 10.7+/−0.7 sequences/block), and a main effect of condition ($F(1,89) = 6.2$, $p < 0.015$), with higher performance for Control than FIDA subjects (13.1+/−0.8 vs. 10.2+/−0.8 sequences/block). There was also a trend for a sex effect ($F(1,89) = 3.51$. $p = 0.06$), with seemingly higher performance in male than female participants (12.8+/−0.7 vs. 10.6+/−0.8 sequences/block). All interaction effects were non-significant (all ps > 0.13).

A similar repeated measure ANOVA conducted on accuracy performance also disclosed a main session effect ($F(1,89) = 6.33$, $p < 0.015$), with better accuracy in Session 2 than in Session 1 (85+/−3% vs. 80+/−3%). All other main and interaction effects were non-significant (all ps > 0.39).

3.3. Relearning (Session 3)

Repeated measure ANOVAs conducted over blocks C2, C12 failed to disclose any significant speed (all ps > 0.13) or accuracy (all ps > 0.35) effects over Session 3 (Fig. 2).

3.4. Overnight (sleep) consolidation effect (Session 3 vs. Session 2)

The repeated measure ANOVA conducted on speed performance (blocks averaged C1 and C2 vs. B1 and B2) disclosed a main session effect ($F(1,89) = 35.4$, $p < 0.0001$), with higher performance in Session 3 than in Session 2 (13.6+/−0.6 vs. 12.6+/−0.6 sequences/block), and a main condition effect ($F(1,89) = 4.0$, $p < 0.05$), with higher performance in Control than FIDA subjects (14.3+/−0.8 vs. 11.9+/−0.8 sequences/block) (Fig. 4A). The condition by session interaction effect was also significant ($F(1,89) = 4.8$, $p < 0.03$). Tukey post-hoc tests evidenced improved overnight performance for FIDA subjects only ($p < 0.015$; Fig. 4A). Additionally, the condition by session by sex interaction effect ($F(1,89) = 4.5$, $p < 0.04$) was significant. Post-hoc tests disclosed a significant overnight performance improvement in FIDA female ($p < 0.02$) but not in FIDA male subjects, whereas performance remained stable overnight in both male and female Controls (Fig. 4B).

Finally, the repeated measure ANOVA conducted on accuracy performance failed to reveal any significant effect (all ps > 0.18), but there was a trend for a condition by session interaction effect ($F(1,89) = 3.6$, $p = 0.06$). Exploratory post-hoc tests suggested an apparently higher accuracy in Session 3 than in Session 2 in FIDA (87+/−4 vs. 84+/−4%; $p = 0.08$) but not Control subjects (85+/−4 vs. 86+/−4%; $p > 0.95$).

3.5. Correlations between overnight performance changes and PSG parameters

Correlations between PSG parameters and the overnight learning effect (ie, [speed performance averaged over blocks C1, C2 minus speed performance averaged over blocks B1, B2]/[speed performance averaged over blocks B1, B2]) were all non-significant (all ps > 0.08).

4. Discussion

The aim of this study was to investigate motor skill learning in FIDA adolescents. Our results show that learning was slower in

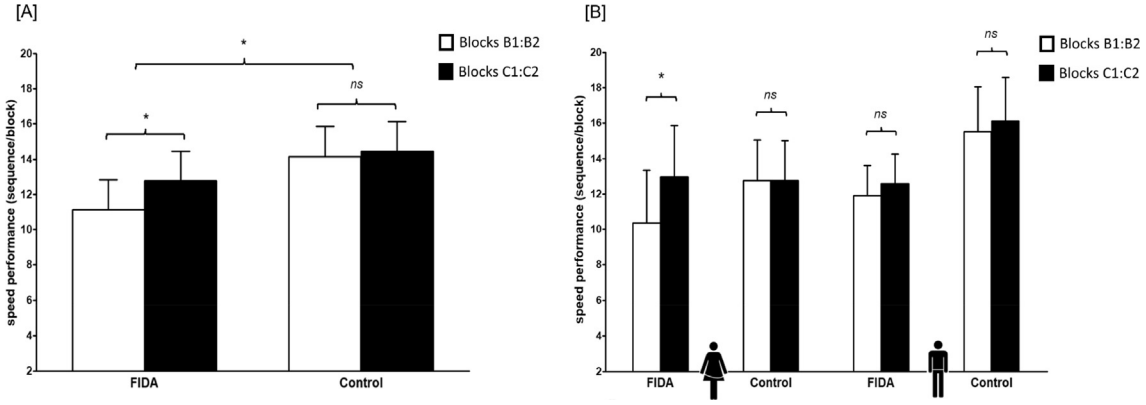

Fig. 4. [A] Overnight sleep effect: summarized speed performance during Session 2 (blocks B1, B2 averaged, white bars) and at the beginning of Session 3 (blocks C1, C2 averaged, black bars). [B] Overnight progression of performance modulated by Sex and Condition: summarized speed performance in male and female FIDA and Control adolescents during Session 2 (blocks B1, B2 averaged, white bars) and at the beginning of Session 3 (blocks C1, C2 averaged, black bars). All data are mean values with 95% confidence interval. Repeated measures ANOVAs; *p < 0.05 **p < 0.001. FIDA: former iron deficient anemic.

FIDA subjects, who eventually reached lower performance levels at the end of the first session. Nonetheless, a similar boost effect was apparent in both populations, even though the FIDA group remained with a reduced achievement level relative to the Control group. Performance after a night of sleep improved in FIDA, but not in Control adolescents who exhibited stabilized performance levels as compared to Session 2; post-hoc analyses revealed that overnight improvement in the FIDA group was present only in female participants.

There might be several mechanisms by which IDA in infancy could affect motor learning abilities. For instance, dopamine is released from the globus pallidus during a motor sequence learning task [33]. Since iron deficiency is associated with altered functioning of the dopamine neurotransmission system [34], such a condition would imply a delayed acquisition of striatum-dependent motor behaviors. The lower performance of FIDA adolescents could be related to the persistent effect of IDA in infancy on the functioning of dopamine circuitry [7]. Furthermore, iron deficiency during early developmental stages disrupts iron processing, storage, or availability, thus eventually affecting myelin quantity, quality, composition, and compaction [3,35]. Myelin alterations can persist even if the iron content achieves normal levels after iron supplementation [36]. Since motor skill learning is achieved when a new neuronal connection is formed, or an existing one is strengthened [37,38], we propose that FIDA adolescents might show alterations in myelin circuitry formation and integrity. Finally, iron deficiency disrupts brain energy metabolism and alters neuronal dendritic mitochondrial structure, and motility [4,5]. These alterations impair the plasticity capacity of spines and synapses [4,39]. Evidence suggests that synaptic plasticity plays a key role in motor learning [40,41]. Hence, these combined effects might contribute to the long-lasting effects of early life iron deficiency on the development of motor learning abilities.

Our findings also show that sleep might influence motor performance in FIDA adolescents, and in particular in female subjects. Gender effects have been reported in sleep-dependent memory consolidation, with overnight memory consolidation being better only at the mid-luteal phase of the menstrual cycle in female participants [42]. Studies have shown a male advantage in motor abilities and spatial cognition performance [23,43]. As information about the phase of the menstrual cycle was not obtained from our participants, this potential effect of the cycle position cannot be estimated in the present study. Notwithstanding, gender-related differences in post-training sleep improvement might also, at least in part, stem from different learning trajectories and sensitivity to training conditions [44,45]. For instance, in female adolescents with ADHD, compared to controls, overnight performance gains in accuracy were found initially dampened in normal learning conditions [44], a gender- and ADHD-related effect that actually disappeared when training sessions were shortened [45]. A lack of gender-related differences between male and female control subjects (as compared to the FIDA condition) might also be because female control subjects were at the same level of performance as male FIDA subjects. This level of performance at the end of learning might have been high enough to prevent further improvement. For example, prior reports found that sleep mostly benefits learning when it is at an intermediate, but not a ceiling level [17].

In addition to gender-related effects, it must be acknowledged that beneficial effects of post-learning sleep for the consolidation of novel skills in procedural memory remain a controversial issue. Whereas some studies found motor skill learning improvement with post-training sleep [46–48], others observed equivalent stabilization or improvement effects after sleep and wakefulness [49,50], or that sleep-related effects are actually modulated by several factors [51]. For instance, sleep was found to induce stronger FTT improvement when associated with anticipated reward [52], or to promote higher gains in tasks featuring a greater degree of motor skill complexity [53]. As mentioned above, our control subjects did not improve after a night of sleep. This suggests that the FTT was relatively easy for them, reaching their learning plateau before sleep, thus preventing further sleep-related improvement [17]. This was not the case in FIDA subjects (in particular, females) who did not achieve ceiling performance during the learning session. In the absence of a waking interval control condition to contrast with the sleep interval, which we acknowledge as a limitation in this study, this interpretation remains tentative and should be explored in further studies. Notwithstanding, there is evidence that sleep can provide a significant benefit in motor learning [46,47], including in adolescents [54].

In conclusion, our findings further confirm that IDA in infancy is associated with altered neurocognitive functioning later on in adolescence. Otherwise, healthy FIDA subjects are characterized by a slower learning performance during wakefulness relative to Control subjects. Furthermore, performance in FIDA adolescents improved after a night of sleep, providing support to the hypothesis that sleep might contribute to compensate for motor learning deficits during the awake training period.

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Conflict of interest

The authors have no conflicts of interest nor financial relationship relevant to this article to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.023.

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