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Acute and Chronic Altitude-Induced Cognitive Dysfunction in Children and Adolescents

Stefano F. Rimoldi, MD[1], Emrush Rexhaj, MD[1], Hervé Duplain, MD[2], Sébastien Urben, MD[3], Joël Billieux, MD[4], Yves Allemann, MD[1], Catherine Romero, RN[5], Alejandro Ayaviri, MD[5], Carlos Salinas, MD[5], Mercedes Villena, MD[5], Urs Scherrer, MD[1,6], and Claudio Sartori, MD[2]

Objective To assess whether exposure to high altitude induces cognitive dysfunction in young healthy European children and adolescents during acute, short-term exposure to an altitude of 3450 m and in an age-matched European population permanently living at this altitude.

Study design We tested executive function (inhibition, shifting, and working memory), memory (verbal, short-term visuospatial, and verbal episodic memory), and speed processing ability in: (1) 48 healthy nonacclimatized European children and adolescents, 24 hours after arrival at high altitude and 3 months after return to low altitude; (2) 21 matched European subjects permanently living at high altitude; and (3) a matched control group tested twice at low altitude.

Results Short-term hypoxia significantly impaired all but 2 (visuospatial memory and processing speed) of the neuropsychological abilities that were tested. These impairments were even more severe in the children permanently living at high altitude. Three months after return to low altitude, the neuropsychological performances significantly improved and were comparable with those observed in the control group tested only at low altitude.

Conclusions Acute short-term exposure to an altitude at which major tourist destinations are located induces marked executive and memory deficits in healthy children. These deficits are equally marked or more severe in children permanently living at high altitude and are expected to impair their learning abilities. *(J Pediatr 2015;■:■-■)*.

Millions of children either live permanently at high altitude or travel to high-altitude tourist destinations. In addition to the well-established altitude-related medical risks,[1] neuropsychological dysfunction may represent a significant problem in these children.[2-6] In adults, short-term hypoxia induces a panoply of behavioral and cognitive alterations,[3,7] including executive difficulties[4,8] and alterations of speed processing and memory.[9,10] Similar alterations have been reported in high-altitude dwellers chronically exposed to lack of oxygen,[11] as well as in patients suffering from diseases associated with chronic hypoxia at low altitude.[12-16] These cognitive alterations, which often go unrecognized by the subject, may have important consequences on mental performance (particularly in complex or stressful situations)[17,18] as demonstrated by the inability of pilots to perform psychomotor tasks after acute exposure to an altitude as low as 2438 m.[19,20] There is very little information on the effects of altitude on cognitive function in children.[21] Similar to adults, children display cerebral hypoxia at altitude[22] and suffer from high-altitude-related diseases,[23,24] even though the clinical presentation of mountain sickness may differ between children and adults.[25,26] To fill this knowledge gap, we examined the effects of acute, short-term (24 hours, Jungfraujoch, Switzerland, 3450 m) and chronic, long-term (>3 years, La Paz, Bolivia, 3500 m) high-altitude exposure on executive function, speed processing, and memory abilities of healthy European children.

Methods

The acute, short-term high-altitude group was composed of 48 healthy Swiss children and adolescents (20 girls and 28 boys) aged between 10 and 17 years (mean ± SD age: 13.6 ± 1.7 years). All participants lived at an altitude <800 m, except for 2 who lived at 1100 m. None of the participants had spent time at altitudes >1500 m during the 2 months preceding the study. Participants ascended to the high-altitude research station at Jungfraujoch, Switzerland, by a 2.5-hour train ride that took them from 568 to 3450 m. On the day of arrival, the participants had a rest and visited the research station. The neuropsychological tests were performed in the afternoon of the second day (24 hours after arrival at high altitude). Three months after the return to low altitude, all tests were repeated (Lausanne University Hospital, 580 m).

AMS	Acute mountain sickness
Corsi Block	Corsi Block Tapping Test
TMT	Trail Making Test

From the [1]Department of Cardiology and Clinical Research, University Hospital, Bern, Switzerland; [2]Department of Internal Medicine, University Hospital, [3]Research Unit, Child and Adolescent Psychiatric Service, University Hospital, Lausanne, Switzerland; [4]Psychological Sciences Research Institute, Catholic University of Louvain, Louvain-la-Neuve, Belgium; [5]Bolivian Institute of Altitude Biology (IBBA), La Paz, Bolivia; and [6]Department of Biology, University of Tarapacá, Arica, Chile

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Because the order of the high- and low-altitude tests was not randomized, an age- (13.7 ± 0.3 years) and sex-matched (7 girls and 7 boys) low-altitude control group living at low altitude (<800 m) was tested twice at low altitude (580 m) with an interval of 3 months, in order to test for a possible learning effect.

The chronic, long-term high-altitude group was composed of 21 healthy European (6 from Switzerland, 5 from Germany, 5 from France, 4 from Spain, and 1 from Italy), children and adolescents (12 girls and 9 boys) aged between 11 and 17 years (mean ± SD age: 14.9 ± 1.7 years) who were born at sea-level and had been permanently living in La Paz, Bolivia (3500 m) for >3 years. The high-altitude exposure of the participants started between the age of 6 months and 6 years. Their parents were mainly working as businessmen, engineers, or embassy personnel.

All participants had a similar education level and cultural and socioeconomic background. The experimental protocol was approved by the institutional review boards on human investigation (Lausanne, Switzerland and La Paz, Bolivia). All participants and their parents provided written informed consent.

All assessments were carried out by a trained psychologist in a quiet testing room. Before starting with the neuropsychological tasks, the general cognitive abilities were assessed using Raven's Progressive Matrices,[27] a nonverbal reasoning test. The 3 groups performed similarly on this task ($P = .353$).

A battery of neuropsychological tests assessing executive functions (inhibition, shifting, and working memory), memory (verbal short-term, verbal episodic, and visuospatial memories), and verbal speed processing ability were administered. The order of the tasks was balanced across participants.

The Attentional Network Task[28] was used to assess the inhibition abilities. An arrow pointing to the left or to the right was presented in the middle of the computer screen. It was surrounded by 4 other arrows (2 on each side of the central arrow), pointing either in the same direction as the central arrow (congruent trials) or in the opposite direction (incongruent trials). Participants had to indicate in which direction the middle arrow pointed by pressing either the left or the right button of the computer mouse as quickly as possible. The inhibition score was calculated as follows: (median reaction time of correct incongruent trials) − (median reaction time of correct congruent trials).

The Trail Making Test (TMT)[29] is a timed pencil-and-paper test composed of 2 parts. Part A was used to assess the speed processing ability. The participants had to connect a series of numbered dots scattered randomly on the page by drawing a line between them. Part B was used to measure the cognitive flexibility (shifting ability). The participants had to connect dots by alternating (shifting) between consecutive numbers and letters. The realization time for each part was recorded separately.

The Digit Span Task[30] consisted of 2 parts. The forward digit span was used to assess the verbal short-term memory ability. Participants had to repeat series of numbers in the same order as presented by the examiner. The backward digit span was used to assess the working memory ability. Participants had to repeat series of numbers presented by the examiner in backward order. For both parts, the length of the series was increased along the trial. For each part, the span representing the longest series of numbers correctly recalled by the subject was used.

The California Verbal Learning Test[31] was used to assess episodic verbal memory. The participants were first presented with 5 learning trials of a list A consisting of 15 words divided into 3 semantic categories (clothes, games, and fruits). The list was read aloud by the examiner, and the participants were asked to recall the words after each trial. Then, the list B, the "interference list" composed of 15 different words was presented for 1 single trial. After the recall of the list B, the participants were asked to recall list A, by free and categorically cued recall (first long-term recall). Ten minutes later, a second free and cued recall of the list A was achieved (second long-term recall). The number of correct words recalled during the first and the second long-term free and cued recalls was registered.

The Corsi Block Tapping Test (Corsi Block)[32] was used to assess the visual-spatial short-term memory ability. The task consisted of a series of 9 blocks arranged irregularly on a board. The blocks were tapped by the examiner in randomized sequences of increasing length. Immediately after each examiner-tapped sequence, the participants attempted to reproduce it, continuing until no longer accurate. The span representing the longest sequence of blocks correctly reproduced by the participant was used.

Statistical Analyses

Paired Student *t* tests were used to compare the performances between the first and the second assessment within the groups. Unpaired Student *t* tests were used to compare the performances between the groups. Data are presented as mean ± SD. A *P* value of <.05 was considered to indicate statistical significance.

Results

Short-term hypoxia induced a significant impairment of 5 of the 7 the abilities that were tested; only visuospatial memory (Corsi Block) and processing speed (TMT part A) were not significantly altered by short-term high-altitude exposure (**Table**). These alterations of cognitive function induced by acute short-term high-altitude exposure were also present or even significantly more severe (visuospatial memory and processing speed) in children permanently living at high altitude.

In the control group tested twice at low altitude, performances were comparable during the first and second assessment, and similar to those observed in the short-term high-altitude exposure group 3 months after return to low altitude.

We found that executive functions were markedly altered at high altitude. During short-term high-altitude exposure,

Table. Cognitive performances at low- and high-altitude in children and adolescents

			Control		Experimental		Experimental		Experimental
			Low altitude (n = 14)	P*	Low altitude (n = 48)	P†	Acute altitude	P‡	Chronic altitude (n = 21)
Executive	Inhibition	ANT (msec)	92.36 (31.03)	.534	93.26 (37.37)	<.001	129.91 (62.25)	.33	148.34 (90.39)
	Shifting	TMT part B (sec)	63.39 (18.52)	.754	66.73 (25.04)	.003	74.92 (28.09)	.77	71.30 (23.77)
	Working memory	Backward span (# digit)	4.96 (1.51)	.968	4.88 (1.36)	.045	4.52 (1.64)	.37	4.627 (1.06)
Memory	Verbal	Digit Span (# digit)	6.15 (1.19)	.724	5.96 (0.99)	.003	5.63 (1.10)	.06	6.33 (1.06)
	Verbal episodic	CVLT (# word)	12.42 (1.55)	.635	13.50 (1.82)	<.001	11.92 (2.47)	.36	10.86 (1.68)
	Visuospatial	Corsi Block (# item)	6.18 (1.09)	.04	6.88 (0.98)	.237	6.69 (1.15)	.008	5.67 (0.86)
Processing	Speed	TMT part A (sec)	25.36 (7.00)	.843	26.07 (7.58)	.085	27.65 (8.14)	.044	32.52 (9.57)

ANT, Attentional Network Task; *CVLT*, California Verbal Learning Test.
Data are presented as mean (SD).
**P* value of unpaired *t* tests between control and experimental groups at low altitude.
†*P* value of paired *t* tests between low altitude and high altitude in the experimental group.
‡*P* value of unpaired *t* tests between acute altitude and chronic altitude in the experimental groups.

the inhibition score on the attention network task was 30% higher ($P < .001$), the time it took to complete part B of the TMT (measuring shifting abilities) was roughly 20% longer ($P = .003$), and the backward digit span (measuring the working memory) was roughly 10% smaller ($P = .045$) compared with low-altitude conditions. All these alterations were also present in subjects permanently living at high altitude (Figure 1).

Both verbal short-term memory and verbal episodic memory were impaired after a 24-hour exposure to high altitude, as evidenced by a significant decrease of the series of numbers recalled during the forward digit span ($P = .003$) and the number of words recalled in the California Verbal Learning Test ($P < .001$) compared with low altitude (Figure 2). In contrast, visuospatial memory (Corsi Block) was not altered during short-term high-altitude exposure ($P = .237$).

Long-term high-altitude exposure had comparable or even more severe effects on memory abilities. Whereas the forward digit span test and episodic verbal memory were not different during short- and long-term high-altitude exposure, the alteration of the visuospatial memory ability was significantly more severe ($P < .01$) during long-term than during short-term high-altitude exposure.

Whereas short-term high-altitude hypoxia had no detectable effect ($P = .085$, low vs acute high altitude) on the time needed to complete part A of the TMT, the time needed to complete this test was >25% longer in subjects permanently living at high altitude ($P = .047$, acute vs long-term high altitude).

Discussion

This study shows the effects of short- and long-term exposure to high altitude on executive, memory, and processing abilities among healthy European children and adolescents born at low altitude. The principal findings were that first, short-term 24-hour exposure to high altitude markedly impaired verbal short-term memory, episodic memory, and executive functions in healthy children, and second and most importantly, similar or even more severe impairments of these functions were also detectable in children who had been permanently living at high altitude for at least 3 years. Finally, the impairments of neuropsychological functions induced by acute short-term high-altitude exposure were no longer detectable 3 months after descent to low altitude. These findings indicate that acute exposure to an altitude at which

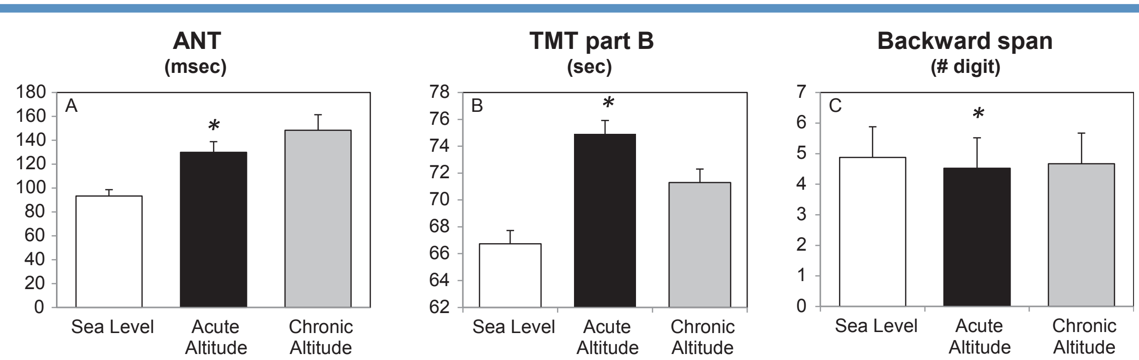

Figure 1. Effects of acute or chronic altitude exposure to 3450 m on **A,** inhibition (Attentional Networks Task [ANT]), **B,** shifting (TMT part B), and **C,** working memory (backward span) abilities in healthy children and adolescents. (N = 48 for acute exposure; N = 21 for chronic exposure). Data are presented as mean ± SE, $^{*}P < .05$ vs sea level.

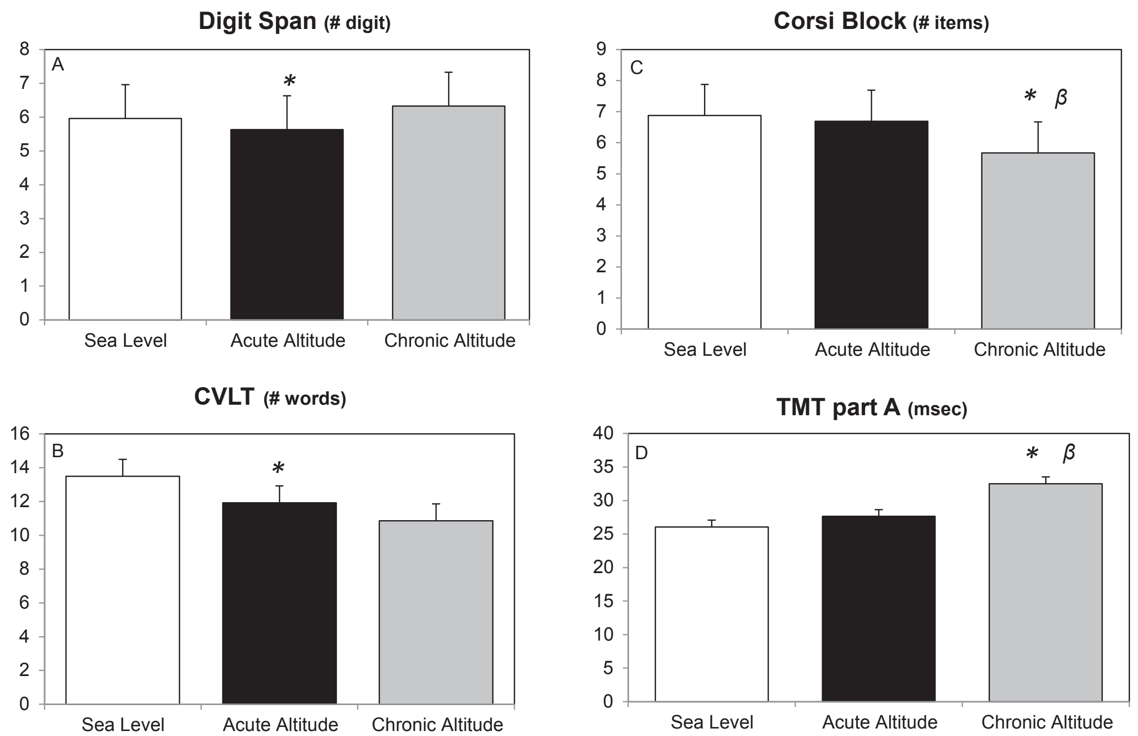

Figure 2. Effects of acute or chronic altitude exposure to 3450 m on **A,** verbal (digit span), **B,** verbal episodic (California Verbal Learning Test [CVLT]), **C,** visuospatial memory (Corsi Block), and **D,** speed processing abilities (TMT part A) in healthy children and adolescents. (N = 48 for acute exposure; N = 21 for chronic exposure). Data are presented as mean ± SE, $^{*}P < .05$ vs sea level; $^{\beta}P < .05$ vs acute altitude.

major tourist destinations are located and permanent living at an altitude where >15 million people live worldwide induces marked alterations of cognitive functions in healthy children and adolescents. The persistence of these alterations in the long-term resident children suggests that there is little or no adaptation of neuropsychological function to high altitude.

Short-term hypoxia induced significant executive dysfunction in these healthy children and adolescents, as evidenced by alteration of inhibition, shifting, and working memory. These alterations of executive function persisted in children permanently living at high altitude and appear to be similar to the alterations reported for adults living at high altitudes.[4,21] At the neuro-anatomical level, these impairments of the executive functions may be related to hypoxia-induced dysfunction of the white cerebral matter,[16,33] perhaps at the level of structures located in the prefrontal cortex, such as the anterior cingulate cortex.[4,34,35]

In regard to the memory abilities, verbal short-term and long-term episodic memories were affected both during acute short-term and long-term exposure to high altitude, whereas visuospatial memory was altered only in participants permanently living at high altitude suggesting greater resistance against the harmful effects of hypoxia of neuronal circuitry regulating the latter.[5] Alternatively, the findings could be related to differences in the sensitivity of the neuropsychological tests used to assess episodic and visuospatial memory tests in our studies.[36] The present observation that, during the episodic memory task at high altitude, children and adolescents were not helped by semantic cues to recall the information suggests that the deficit was mainly caused by primary encoding difficulties. This observation contrasts with findings in adults who rarely present episodic deficits at high altitude.[4] This could suggest that hippocampal structures involved in episodic memory[37,38] may be more sensitive to the effects of hypoxia in children and adolescents than in adults.

Finally, speed processing abilities were altered during only long-term, but not acute short-term altitude exposure. In contrast, in adults, speed processing deficits were reported already at modest altitude (2500 m) and during short-term hypoxia.[9,39] Taken together, these findings suggest that during hypoxia, speed processing abilities are better preserved in children than in adults.

In the participants exposed to short-term hypoxia, the significant neuropsychological deficits were reversible upon return to normoxia at low altitude. In line with this observation, cognitive deficits induced by intermittent hypoxia in children disappear with appropriate medical treatment.[40] In contrast, more severe hypoxia during early life in children born prematurely is associated with a persistent impairment of executive functions throughout childhood.[41] This could suggest that the timing of hypoxia may be an important determinant of its long-term neuropsychological consequences in children. Further studies are needed to examine the relationships between the timing and duration of a hypoxic insult in children and its long-term consequences on cognitive functions later in life.

The present data on the effects on cognitive function of short- and long-term altitude exposure may shed some light on the neuropsychological effects of chronic and/or intermittent hypoxia in patients living at low altitude. Among children suffering from diseases associated with chronic hypoxemia, there is evidence that cognitive performances are impaired.[35,42,43] The present experimental findings confirm and extend these earlier observational data. They suggest that the hypoxia-induced impairments in cognitive functions occur rapidly and may involve different anatomic structures in specific ways. Most importantly, the present data in healthy children permanently living at high altitude suggest that cognitive alterations induced by hypoxia persist without undergoing any apparent signs of adaptation. Consistent with this concept, recent data provided by Virues-Ortega et al[44] show that Bolivian children born and living in La Paz (3700-4100 m) suffer from impaired neuropsychological functioning possibly related to loss of cerebral blood flow autoregulation at high altitude.[44]

In adults, cognitive function has not been assessed with acclimatization frequently, but when such has been examined, adults appear able to restore some aspects of cognitive function (particularly reaction time) to sea level values after 2 weeks at altitude >5000 m.[45]

Interestingly, the slowdown of neural processing in high altitude dwellers has been interpreted by some authors as an adaptive, rather than a deficient trait, perhaps enabling accuracy of mental activity under hypoxic conditions.[11] Consistent with this speculation, others have proposed that subjects exposed to chronic hypoxia tend to sacrifice some specific neuropsychological performances such as reaction time/processing speed in order to maintain accuracy in performing more important and complex cognitive tasks.[46]

The comparison between short- and long-term high altitude exposure in our study also allows 2 additional observations. First, neuropsychological impairments were not more severe in children ascending very rapidly (within 2 1/2 hours) to 3450 m than in children chronically exposed to altitude. Second, none of the participants suffered from acute/chronic altitude related-disease at the time the neuropsychological tests were performed. Taken together these observations suggest that the rapidity of the ascent and the presence of acute mountain sickness (AMS) are not essential determinants of altitude-related executive and memory impairments. Consistent with this concept, neuropsychological alterations associated with AMS were found to be different from those induced by hypoxia.[6] More importantly, prevention of AMS with acetazolamide was associated with impaired rather than improved neuropsychological performances in adults exposed to 3500 m.[47]

Finally, the neuropsychological impairment in children in the present study was more severe than the one reported in adults studied at 5100 m[48] suggesting that children may be more sensitive than adults to altitude-induced neuropsychological alterations.

The clinical relevance of the neuropsychological alterations observed in the present study is difficult to evaluate. The participants looked comfortable and fit and behaved normally during the examinations. The altered performances would certainly have undergone undetected without specific testing. Nevertheless, the magnitude of the observed impairments appears similar to the deficit observed in collegiate hockey players who were victims of head concussion.[49]

In conclusion, short-term exposure of healthy children and adolescents to an altitude at which major tourist destinations are located induced significant memory and executive deficits. These deficits are reversible after return to low altitude normoxia, but persist or even are more obvious in children permanently living at high altitude. We speculate that learning new information at high altitude may be particularly difficult because not only the encoding but also the retrieval processing was altered. Based on these findings, the study of the learning abilities of children born and permanently living at high altitude appears of utmost importance. ■

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Reprint requests: Claudio Sartori, MD, Department of Internal Medicine, Centre Universitaire Hospitalier Vaudois, BH 10.640, 1011 Lausanne-CHUV, VD-Switzerland. E-mail: Claudio.Sartori@chuv.ch

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