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

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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 2016;169:238-43)*.

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).

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

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Three months after the return to low altitude, all tests were repeated (Lausanne University Hospital, 580 m).

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-