Title: Acute and Chronic Altitude-Induced Cognitive Dysfunction in Children and Adolescents.

Authors: Rimoldi SF, Rexhaj E, Duplain H, Urben S, Billieux J, Allemann Y, Romero C, Ayaviri A, Salinas C, Villena M, Scherrer U, Sartori C

Journal: The Journal of pediatrics

Year: 2016 Feb

Volume: 169

Pages: 238-43

DOI: 10.1016/j.jpeds.2015.10.009

Acute and chronic altitude-induced cognitive dysfunction in children and adolescents

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

[1] Swiss Cardiovascular Center, University Hospital, Bern,

[2] Department of Internal Medicine, CHUV, Lausanne, and

[3] Research Unit, Child and Adolescent Psychiatric Service, CHUV, Lausanne, all in Switzerland

[4] Psychological Sciences Research Institute, Catholic University of Louvain, Louvain-la-Neuve, Belgium

[5] Instituto Boliviano de Biologia de Altura, La Paz, Bolivia

[6] Facultad de Ciencias, Departemento de Biología, Universidad de Tarapacá, Arica, Chile

Corresponding Author:

Dr. Claudio Sartori, Department of Internal Medicine, Centre Universitaire Hospitalier Vaudois, BH 10.640, 1011 Lausanne-CHUV, VD- Switzerland.

Phone: +4121 3140930, Fax : +4121 3140928, Email : Claudio.Sartori@chuv.ch

Conflict of interest: There are no financial or other relations that could lead to a conflict of interest.

No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

ABSTRACT

Objective: Millions of people including families with children are being exposed to high-altitude related medical risks. Among these risks, altitude-induced cognitive dysfunction may represent an important problem, but, surprisingly, there is no information on cognitive abilities in children at high altitude. To provide such information, we assessed neuropsychological abilities in young healthy European children and adolescents during acute, short-term exposure to 3450 m and in an age-matched European population permanently living at this altitude.

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

Results: Short-term hypoxia significantly impaired all but two (visuo-spatial memory, 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 to those observed in the control group tested only at low altitude

Conclusion: 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.

INTRODUCTION

Millions of children either permanently live 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 behavioural and cognitive alterations (3, 7) including executive difficulties (4, 8) and alterations of speed processing and memory.(9, 10) Similar alteration 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 performances (particularly in complex or stressful situations) (17, 18) as demonstrated by the inability of pilots to perform psychomotor task after acute exposure to an altitude as low as 2438 m.(19, 20)

Interestingly, there is very little information on the effects of altitude on cognitive function in children.(21) This is surprising since, like 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 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, speed processing and memory abilities of healthy European children.

METHODS

Participants

Acute, short-term high altitude studies. The 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 were living 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 the 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). 3 months after the return to low altitude all tests were repeated (Lausanne University Hospital, 580 m).

Low altitude control studies. Since the order of the high- and low-altitude test was not randomised, an age- (13.7 ± 0.3 years) and sex-matched (7 girls and 7 boys) 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.

Chronic, long-term high altitude studies. The 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 (3500m) for >3 years. The high-altitude exposure in 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 socio-economical 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.

Procedure and Materials

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 non-verbal 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 visuo-spatial memories) and verbal speed processing ability were administered. The order of the tasks was balanced across participants.

*Attentional Networks Tas*k.(28) This test was used to assess the inhibition abilities. An arrow pointing left- or right-wards was presented in the middle of the computer screen. It was surrounded by four other arrows (two 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).

Trail Making Test.(29) This test is a timed pencil-and-paper test composed of two 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 realisation time for each part was recorded separately.

Digit Span. (30) The task consisted of two 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.

California Verbal Learning Test. (31) This test 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, 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 one single trial. After the recall of the list B, the participants were asked to recall the list A, by free and categorical-cued recall (first long-term recall). Ten minutes later, a second free and cued recall of the list A was realised (second long-term recall). The number of correct words recalled during the first and the second long-term free and cued recalls was registered.

Corsi Block Tapping. (32) This test was used to assess the visual-spatial short-term memory ability. The task consisted of a series of nine 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 Analysis

Paired Student's *t*-tests were used to compare the performances between the first and the second assessment within the groups. Unpaired student's *t*-tests were used to compare the performances between the groups Data are presented as mean±SD. A P value <0.05 was considered to indicate statistical significance.

RESULTS

The main results are summarized in the Table.

Short-term hypoxia induced a significant impairment of 5 of the 7 the abilities that were tested; only visuo-spatial memory (Corsi block) and processing speed (TMT part A) were not significantly altered by short-term high altitude exposure. These alterations of cognitive function induced by acute short-term high altitude exposure were also present or even significantly more severe (visuo-spatial 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 1st and 2nd assessment, and similar to those observed in the short-term high altitude exposure group 3 months after return to low altitude.

Executive functions: We found that executive functions were markedly altered at high altitude. During short-term high altitude exposure the inhibition score on the Attention Network Task was 30 percent higher ($P<0.001$), the time it took to complete part B of the Trail Making Test (measuring shifting abilities) was roughly 20 percent longer ($P=0.003$), and the backward digit span (measuring the working memory) was roughly 10 percent smaller ($P=0.045$) compared to low altitude. All these alterations were also present in subjects permanently living at high altitude. (Figure 1)

Memory abilities: Both verbal short-term memory and verbal episodic memory were impaired after 24-h exposure to high-altitude, as evidenced by a significant decrease of the series of numbers recalled during the forward digit span ($P=0.003$) and the number of words recalled in the California Verbal Learning Test ($P<0.001$) compared with low altitude (Figure 2). In contrast, visio-spatial memory (Corsi Block Tapping Test) 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 visuo-spatial memory

ability was significantly more severe (*P<0.01*) during long-term than during short term-high altitude exposure.

Speed processing ability: 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 Trail Making Test, the time needed to complete this test >25% longer in subjects permanently living at high altitude (P=0.047, acute vs. long-term high altitude).

Discussion

This study shows for the first time the effects of short- and long-term exposure to high altitude on executive, memory and processing abilities of healthy European children and adolescents born at low altitude. The main new 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 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 adult high altitude dwellers.(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) particularly at the level of structures located in the prefrontal cortex, such as the anterior cingulated cortex.(4, 34, 35)

With 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 visuo-spatial 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 visuo-spatial 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 observations contrast 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 only altered during long-term, but not during 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 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. There is evidence that, in children suffering from diseases associated with chronic hypoxemia, 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 involve different anatomical 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. show that Bolivian children born and living in La Paz (3700-4100m) suffer of 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 it has been looked at, it seems that adults can return some aspects of cognitive function (particularly reaction time) to sea level values after two weeks >5000 meters.(45)

Interestingly, the slowing down 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 two additional observations. First, neuropsychological impairments were not more severe in children ascending very rapidly (within 2 1/2 hours) to 3450m than in children chronically exposed to altitude. Second, none of the participants suffered of 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 acute mountain sickness 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 5100m (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 one 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, since 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.

References

1. Hackett PH, Roach RC. High-altitude illness. N Engl J Med. 2001;345(2):107-14.

2. Shukitt-Hale B, Banderet LE, Lieberman HR. Elevation-dependent symptom, mood, and performance changes produced by exposure to hypobaric hypoxia. Int J Aviat Psychol. 1998;8(4):319-34.

3. Bahrke MS, Shukitt-Hale B. Effects of altitude on mood, behaviour and cognitive functioning. A review. Sports Med. 1993;16(2):97-125.

4. Virues-Ortega J, Buela-Casal G, Garrido E, Alcazar B. Neuropsychological functioning associated with high-altitude exposure. Neuropsychol Rev. 2004;14(4):197-224.

5. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. Lancet Neurol. 2009;8(2):175-91.

6. Yan X. Cognitive impairments at high altitudes and adaptation. High Alt Med Biol. 2014;15(2):141-5.

7. Hopkins RO, Haaland KY. Neuropsychological and neuropathological effects of anoxic or ischemic induced brain injury. J Internat Neuropsychol Soc : JINS. 2004;10(7):957-61.

8. Kida M, Imai A. Cognitive performance and event-related brain potentials under simulated high altitudes. J Appl Physiol. 1993;74(4):1735-41.

9. Denison DM, Ledwith F, Poulton EC. Complex reaction times at simulated cabin altitudes of 5,000 feet and 8,000 feet. Aerospace Med. 1966;37(10):1010-3.

10. Kramer AF, Coyne JT, Strayer DL. Cognitive function at high altitude. Human factors. 1993;35(2):329-44.

11. Hogan AM, Virues-Ortega J, Botti AB, Bucks R, Holloway JW, Rose-Zerilli MJ, et al. Development of aptitude at altitude. Develop Sci. 2010;13(3):533-44.

12. Antonelli Incalzi R, Marra C, Giordano A, Calcagni ML, Cappa A, Basso S, et al. Cognitive impairment in chronic obstructive pulmonary disease--a neuropsychological and spect study. J Neurol. 2003;250(3):325-32.

13. Grant I, Heaton RK, McSweeny AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med. 1982;142(8):1470-6.

14. Incalzi RA, Gemma A, Marra C, Muzzolon R, Capparella O, Carbonin P. Chronic obstructive pulmonary disease. An original model of cognitive decline. Am Rev Respir Dis. 1993;148(2):418-24.

15. Ozge C, Ozge A, Unal O. Cognitive and functional deterioration in patients with severe COPD. Behav Neurol. 2006;17(2):121-30.

16. Vichinsky EP, Neumayr LD, Gold JI, Weiner MW, Rule RR, Truran D, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA. 2010;303(18):1823-31.

17. Asmaro D, Mayall J, Ferguson S. Cognition at altitude: impairment in executive and memory processes under hypoxic conditions. Aviat Space Environ Med. 2013;84(11):1159-65.

18. Kelman GR, Crow TJ. Impairment of mental performance at a simulated altitude of 8,000 feet. Aerospace Med. 1969;40(9):981-2.

19. Ernsting J. Mild hypoxia and the use of oxygen in flight. Aviat Space Environ Med. 1984;55(5):407-10.

20. Auten JD, Kuhne MA, Walker HM, 2nd, Porter HO. Neurologic decompression sickness following cabin pressure fluctuations at high altitude. Aviat Space Environ Med. 2010;81(4):427-30.

21. Virues-Ortega J, Garrido E, Javierre C, Kloezeman KC. Human behaviour and development under high-altitude conditions. Develop Sci. 2006;9(4):400-10.

22. Yaron M, Niermeyer S, Lindgren KN, Honigman B, Strain JD, Cairns CB. Physiologic response to moderate altitude exposure among infants and young children. High Alt Med Biol. 2003;4(1):53-9.

23. Carpenter TC, Niermeyer S, Durmowicz AG. Altitude-related illness in children. Curr Probl Pediatr. 1998;28(6):177-98.

24. Pollard AJ, Niermeyer S, Barry P, Bartsch P, Berghold F, Bishop RA, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. High Alt Med Biol. 2001;2(3):389-403.

25. Rexhaj E, Garcin S, Rimoldi SF, Duplain H, Stuber T, Allemann Y, et al. Reproducibility of acute mountain sickness in children and adults: a prospective study. Pediatrics. 2011;127(6):e1445-8.

26. Rehakova P, Rexhaj E, Farron F, Duplain H. [Children and pregnant women at high altitude]. Rev Med Suisse. 2014;10(429):1024-7.

27. Raven J. The Raven's progressive matrices: change and stability over culture and time. Cognitive Psychol. 2000;41(1):1-48.

28. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. J Cognitive Neurosci. 2002;14(3):340-7.

29. Reitan RM, Wolfson D. The use of serial testing in evaluating the need for comprehensive neuropsychological testing of adults. Appl Neuropsychol. 2008;15(1):21-32.

30. Kaufmann PM, Fletcher JM, Levin HS, Miner ME, Ewing-Cobbs L. Attentional disturbance after pediatric closed head injury. J Child Neurol. 1993;8(4):348-53.

31. Yeates KO, Blumenstein E, Patterson CM, Delis DC. Verbal learning and memory following pediatric closed-head injury. J Internatl Neuropsychol Soc : JINS. 1995;1(1):78-87.

32. D'Agati E, Cerminara C, Casarelli L, Pitzianti M, Curatolo P. Attention and executive functions profile in childhood absence epilepsy. Brain & development. 2012;34(10):812-7.

33. Allin MP, Kontis D, Walshe M, Wyatt J, Barker GJ, Kanaan RA, et al. White matter and cognition in adults who were born preterm. PLoS One. 2011;6(10):e24525.

34. Yan X, Zhang J, Gong Q, Weng X. Adaptive influence of long term high altitude residence on spatial working memory: an fMRI study. Brain and cognition. 2011;77(1):53-9.

35. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11(1):1-16.

36. Kryskow MA, Beidleman BA, Fulco CS, Muza SR. Performance During Simple and Complex Military Psychomotor Tasks at Various Altitudes. Aviat Space Envir Md. 2013;84(11):1147-52.

37. Lee JK, Ekstrom AD, Ghetti S. Volume of hippocampal subfields and episodic memory in childhood and adolescence. Neuroimage. 2014;94:162-71.

38. Smith ML, McAndrews MP. The hippocampus and episodic memory in children. Journal of the International Neuropsychological Society : JINS. 2013;19(10):1027-30.

39. de Aquino Lemos V, Antunes HK, dos Santos RV, Lira FS, Tufik S, de Mello MT. High altitude exposure impairs sleep patterns, mood, and cognitive functions. Psychophysiol. 2012;49(9):1298-306.

40. Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. Eur Respir J. 2005;25(2):336-42.

41. Newman JB, Debastos AG, Batton D, Raz S. Neonatal respiratory dysfunction and neuropsychological performance at the preschool age: a study of very preterm infants with bronchopulmonary dysplasia. Neuropsychol. 2011;25(5):666-78.

42. Raman L, Georgieff MK, Rao R. The role of chronic hypoxia in the development of neurocognitive abnormalities in preterm infants with bronchopulmonary dysplasia. Develop Sci. 2006;9(4):359-67.

43. Matos SM, Sarmento S, Moreira S, Pereira MM, Quintas J, Peixoto B, et al. Impact of fetal development on neurocognitive performance of adolescents with cyanotic and acyanotic congenital heart disease. Congenital heart disease. 2014;9(5):373-81.

44. Virues-Ortega J, Bucks R, Kirkham FJ, Baldeweg T, Baya-Botti A, Hogan AM, et al. Changing patterns of neuropsychological functioning in children living at high altitude above and below 4000 m: a report from the Bolivian Children Living at Altitude (BoCLA) study. Develop Sci. 2011;14(5):1185-93.

45. Subudhi AW, Bourdillon N, Bucher J, Davis C, Elliott JE, Eutermoster M, et al. AltitudeOmics: the integrative physiology of human acclimatization to hypobaric hypoxia and its retention upon reascent. PLoS One. 2014;9(3):e92191.

46. Cahoon RL. Simple Decision-Making at High-Altitude. Ergonomics. 1972;15(2):157-63.

47. Wang J, Ke T, Zhang X, Chen Y, Liu M, Chen J, et al. Effects of acetazolamide on cognitive performance during high-altitude exposure. Neurotox and teratol. 2013;35:28-33.

48. Harris GA, Cleland J, Collie A, McCrory P. Cognitive assessment of a trekking expedition to 5100 m: a comparison of computerized and written testing methods. Wilderness Environ Med. 2009;20(3):261-8.

49. Pedersen HA, Ferraro FR, Himle M, Schultz C, Poolman M. Neuropsychological Factors Related to College Ice Hockey Concussions. Am J Alzheimers Dis. 2014;29(3):201-4

Figures Legends

Figure 1: Effects of acute or chronic altitude exposure to 3450m on inhibition (Attentional Networks Task, Panel A), shifting (Trail Making Test Part B, Panel B) and working memory (Backward Digit Span, Panel C) abilities in healthy children and adolescents. (N= 48 for acute exposure; N= 21 for chronic exposure). Data are presented as mean ± standard error, * P <.05 vs. Sea Level

Figure 2:**:** Effects of acute or chronic altitude exposure to 3450m on verbal (Digit Span, panel A), Verbal episodic (California Verbal Learning Test, panel B), and visuo-spatial memory (Corsi Block, panel C), as well as speed processing abilities (TMT part A, panel D) in healthy children and adolescents. (N= 48 for acute exposure; N= 21 for chronic exposure). Data are presented as mean ± standard error, * P <.05 vs. Sea Level; P<.β 05 vs. Acute Altitude.

			Control Low Altitude (n = 14)	P^1	Experimental Low Altitude (n = 48)	P^2	Experimental Acute Altitude	P^3	Experimental Chronic Altitude (n = 21)
Executive	Inhibition	ANT (msec)	92.36 (31.03)	*0.534*	93.26 (37.37)	*< .001*	129.91 (62.25)	*0.33*	148.34 (90.39)
	Shifting	TMT Part B (sec)	63.39 (18.52)	*0.754*	66.73 (25.04)	*0.003*	74.92 (28.09)	*0.77*	71.30 (23.77)
	Working Memory	Backward Span (# digit)	4.96 (1.51)	*0.968*	4.88 (1.36)	*0.045*	4.52 (1.64)	*0.37*	4.627(1.06)
Memory	Verbal	Digit Span (# digit)	6.15 (1.19)	*0.724*	5.96 (0.99)	*0.003*	5.63 (1.10)	*0.06*	6.33 (1.06)
	Verbal Episodic	CVLT (# word)	12.42 (1.55)	*0.635*	13.50 (1.82)	*< .001*	11.92 (2.47)	*0.36*	10.86 (1.68)
	Visuo-spatial	Corsi Block (# item)	6.18 (1.09)	*0.04*	6.88 (0.98)	*0.237*	6.69 (1.15)	*0.008*	5.67 (0.86)
Processing	Speed	TMT Part A (sec)	25.36 (7.00)	*0.843*	26.07 (7.58)	*0.085*	27.65 (8.14)	*0.044*	32.52 (9.57)

Data are presented as mean (SD); P^1-value of unpaired t-tests between Control and Experimental groups at Low Altitude. P^2-value of paired t-tests between Low Altitude and High Altitude in the experimental group. P^3-value of unpaired t-tests between Acute Altitude and Chronic Altitude in the experimental groups. TMT: trail making test; CVLT: california verbal learning test; ANT: attentional network task.

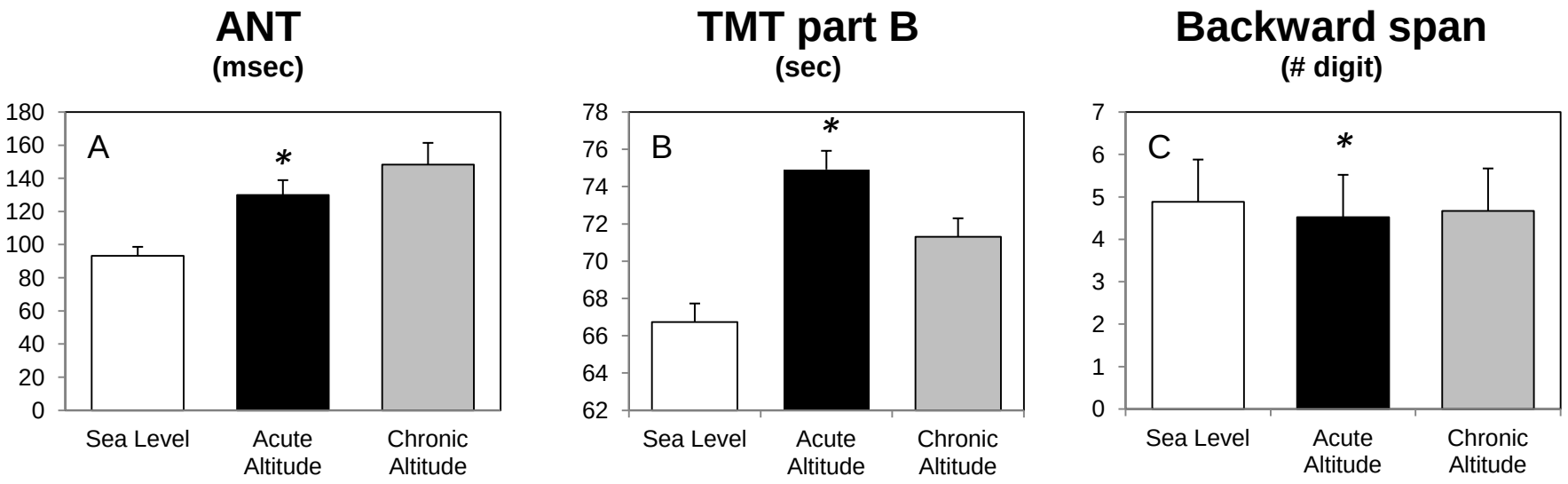
ANT
(msec)
A
*
180
160
140
120
100
80
60
40
20
0
Sea Level
Acute Altitude
Chronic Altitude
TMT part B
(sec)
B
*
78
76
74
72
70
68
66
64
62
Sea Level
Acute Altitude
Chronic Altitude
Backward span
(# digit)
C
*
7
6
5
4
3
2
1
0
Sea Level
Acute Altitude
Chronic Altitude

Figure 1

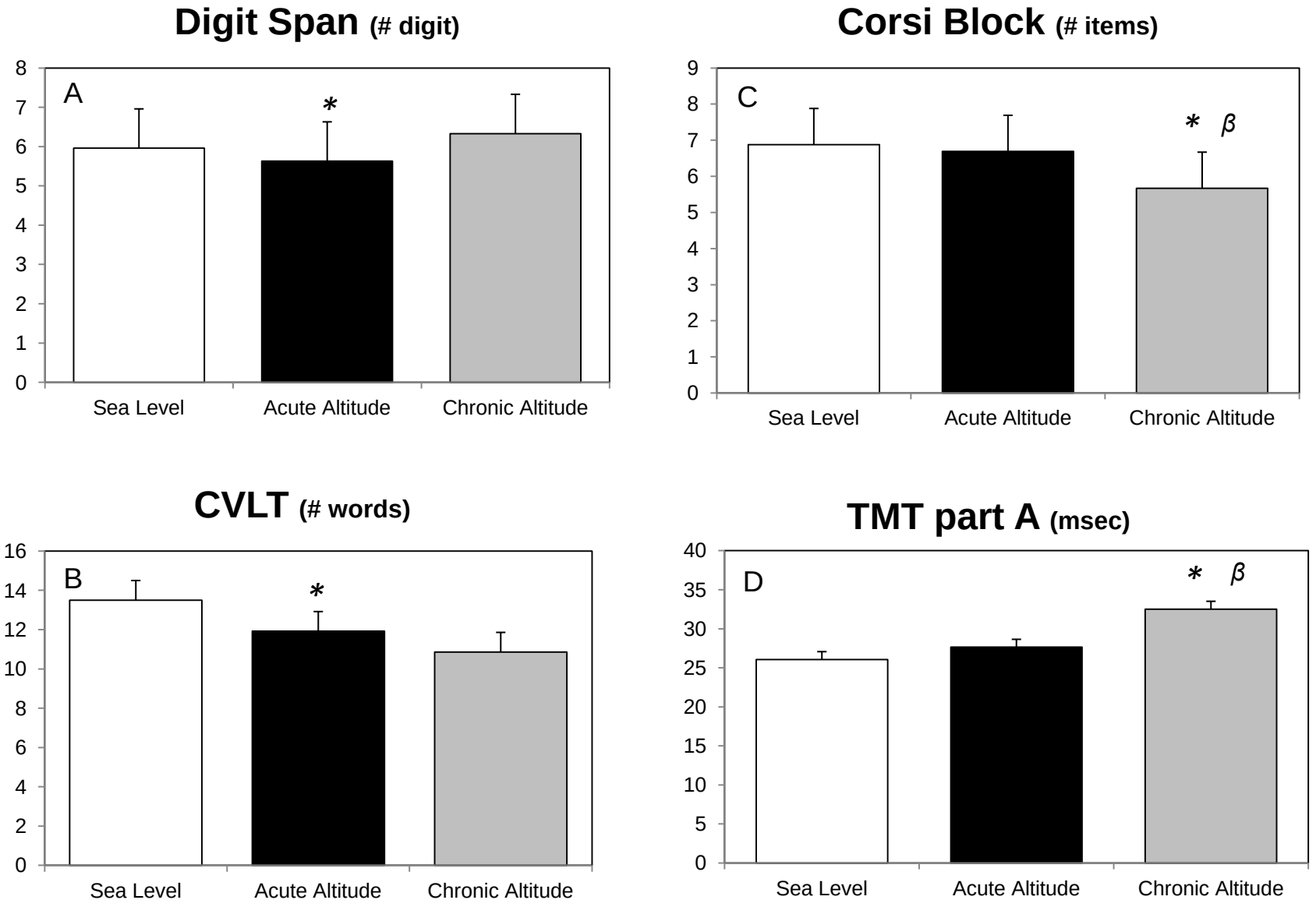
Digit Span (# digit)
A
*
Sea Level
Acute Altitude
Chronic Altitude
Corsi Block (# items)
C
* β
Sea Level
Acute Altitude
Chronic Altitude
CVLT (# words)
B
*
Sea Level
Acute Altitude
Chronic Altitude
TMT part A (msec)
D
* β
Sea Level
Acute Altitude
Chronic Altitude

Figure 2