Short-term high-altitude pre-exposure improves neurobehavioral ability

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This study aims to evaluate the effect of the duration of high-altitude (HA) pre-exposure on human neurobehavioral parameters including mood states and cognitive performance at HA. One hundred and eleven healthy individuals (ranging in age from 18 to 35 years) were recruited to participate in this study. They were divided into two groups: a 4-day short-term HA pre-exposure group ($n = 57$) and a 3-month long-term HA pre-exposure group ($n = 54$). All participants lived in the area at 400 m altitude above sea level before pre-exposure to HA. They were then transported to 3700 m plateau for either a 4-day or a 3-month HA pre-exposure, and finally delivered to 4400 m plateau. On the last day of pre-exposure at 3700 m and on the 10th day at 4400 m, neurobehavioral parameters of the participants in the two groups were evaluated. At the end of pre-exposure and on the 10th day of HA exposure, participants in the short-term group had significantly lower negative mood states, better cognitive performance with higher sensorimotor, attention, and psychomotor abilities, and less acute mountain sickness in comparison with the participants in the long-term pre-exposure group. Our field study with large samples showed that in comparison with 3-month long-term pre-exposure, 4-day short-term HA pre-exposure at 3700 m has a better effect in improving human neurobehavioral parameters including mood states and cognitive performance and reducing acute mountain sickness when exposed to a HA at 4400 m. NeuroReport 27:367–373 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

High-altitude (HA) sickness and neurobehavioral dysfunctions such as negative mood states and inefficient cognitive performance often occur when individuals are exposed to a HA [1,2]. Individuals spending long-term periods at HA and some of the local HA residents could also develop chronic mountain sickness with severe symptomatic polycythemia and hypoxemia [3]. However, HA residents have a much lower rate of short-term acute mountain sickness (AMS) and better cognitive performance than residents of plain areas when exposed to a HA [4]. AMS and impaired neurobehavioral function caused by HA exposure consequently affect missions of medical assistance and military emergency support. Thus, exploration of effective approaches to minimize AMS and neurobehavioral dysfunction at HA is very important to improve operational capability in particular emergency military support and medical rescue missions, which require high positive mood state and powerful cognitive performance.

Several approaches have been developed to minimize the incidence of AMS: (a) neurochemical approach, which includes medications with arterial chemoreceptors when exposed at HA, as the chemoreceptors can increase ventilation and oxygen intake and enhance acclimatization to hypoxia at the early stage [5–8]. (b) Psychological approach, which involves training to become familiar with the challenge and outcomes at HA. (c) Pre-exposure approach, in which individuals spend several days at intermediate HA (around 3000 m) before moving to a HA above 4000 m [9]. It is reported that HA pre-exposure can improve cognitive performance [10,11] and reduce the occurrence of AMS [12,13]. The effect of HA pre-exposure on cognitive performance involves the imbalanced expression of choline acetyltransferase/acetyl cholinesterase in the septal area, piriform and visual cortexes, and the hippocampal CA1 area [14]. The human body has the ability to gradually achieve stable acclimatization by neurohormone regulation and polycythemia [15,16], and the incidence of AMS will decrease when HA pre-exposure time increases [12]. However, prolonged HA pre-exposure (for instance 3–6 months) may also damage cognitive performance and increase the incidence of anxiety [17–19]. Therefore, we hypothesize that short-term HA pre-exposure (STP) within several

days may have more beneficial effects in minimizing the impairment in human neurobehavioral activities when exposed to a HA. Here, we report that a 4-day STP is better than a 3-month long-term HA pre-exposure (LTP) to improve neurobehavioral parameters by promoting mood state and enhancing cognitive performance, in particular, attention ability and when exposed to a HA in a field study with large numbers of participants. We propose that STP could provide a new approach for minimizing HA-induced neurobehavioral disability and AMS.

Materials and methods
Participants
One hundred and eleven healthy individuals serving in the military (ranging in age from 18 to 35 years) were recruited between March 2012 and April 2012 at the army camp in Chongqing city in China to participate in this study. The participants were all men, low-altitude (sea level 400 m) residents, had not been exposed to HA (>2000 m) in the previous year, and had not performed a similar neurobehavioral test. The demographic data on age, height, weight, education level, and smoking and drinking habits, heart rate, and blood pressure were collected before pre-exposure to HA. This study was approved by the Ethics Committee of the Xinqiao Hospital, The Third Military Medical University, Chongqing, China. Written informed consent was obtained from all participants.

Assessments
The participants were divided into two groups: 4-day short-term HA pre-exposure (STP) group ($n = 57$) and 3-month long-term HA pre-exposure (LTP) group ($n = 54$). All participants lived in the plain area at 400 m above sea level. They were transported by plane (flight time < 2.5 h) to 3700 m plateau for either a 4-day or a 3-month HA pre-exposure. After completion of pre-exposure, they were delivered to 4400 m plateau by truck (travel time < 2.5 h). Both groups were informed of the same expectations and motivations about their tasks at 4400 m altitude. On the last day of pre-exposure at 3700 m and on the 10th day at 4400 m, the profiles of mood states and cognitive performance were evaluated and scored. Mood states included vigor-activity (VA) (score between 0 and 32), fatigue-inertia (FI; score 0–32), anger-hostility (AH; score 0–48), depression-dejection (DD; score 0–60), tension-anxiety (TA; score 0–36), and confusion-bewilderment (CB; score 0–28). Cognitive performance included complex reaction time (CRT) (score > 0), digit span (score 0–28), digit symbol (score 0–115), attention span (score 0–63), and pursuit aiming (score 0–420). The assessment on mood states questionnaire and neurobehavioral tests were performed between 8:00 a.m. and noon following the instructions of the Neurobehavioral Core Test Battery (WHO) [20,21].

Table 1 Characteristics of participants ($n = 111$)

	STP ($n = 57$)	LTP ($n = 54$)	P value
Age (years)	22.18 ± 2.12	22.38 ± 1.57	0.823
BMI (kg/m^2)	22.06 ± 1.99	22.12 ± 1.69	0.856
Schooling (years)	11.62 ± 2.01	11.87 ± 2.09	0.871
Smoking rate (%)	69.00	65.20	0.416
Drinking rate (%)	4.80	4.10	0.634
Blood pressure (mmHg)			
SBP	115.17 ± 2.46	117.14 ± 2.25	0.621
DBP	75.98 ± 1.59	73.86 ± 1.40	0.771
Heart rate (beats/min)	69.39 ± 1.33	66.22 ± 1.17	0.576

DBP, diastolic blood pressure; LTP, long-term pre-exposure; SBP, systolic blood pressure; STP, short-term pre-exposure.

Participants completed the tests in a quiet environment without any disturbances.

The CRT was assessed as each participant's reaction ability [22]. The short-term auditory memory ability was evaluated as digit span using the Wechsler Adult Intelligence Scale (WAIS-R) version of digit span (Wechsler, 1981) and the Wechsler memory scale [23,24]. Sensorimotor ability was evaluated as digit symbol using the Wechsler Adult Intelligence Scale (WAIS-R) version of digit symbol [23]. Pursuit aiming represented as participants' movement stability was evaluated using a psychomotor test [25]. Finally, attention span was used to evaluate attention ability [26]. The scores were reported as raw values, and the scores of positive mood state (VA) and negative mood states including FI, AH, DD, TA, and CB were calculated. The AMS score was the total score of headache, gastrointestinal symptoms, fatigue and/or weakness, dizziness/lightheadedness, and difficulty sleeping on the basis of the Lake Louise Score for the diagnosis of AMS (score range 0–15) [21]. A total score between 3 and 5 is considered mild AMS and a score of 6 or more is considered severe AMS.

Statistical analysis
All data were presented as mean ± SEM. Data on mood states, cognitive performance, and AMS at 400, 3700, and 4400 m altitudes in STP and LTP groups were analyzed by two-way analysis of variance using SAS 9.1.3 software (SAS Institute Inc., Cary, North Carolina, USA). The statistical significance of correlation was adjusted by Bonferroni's correction. Student's t-test was used for the comparison of demographic data at 400 m altitude between STP and LTP groups. P less than 0.05 was considered statistically significant (*$P < 0.05$ comparison between STP and LTP groups at the same altitude; #$P < 0.05$ comparison between 400 and 3700 or 4400 m in the same group; and $\Delta P < 0.05$ comparison between 3700 and 4400 m in the same group).

Results
Short-term HA pre-exposure minimized negative mood states
To test our hypothesis that STP could have better effects to minimize the impairment of neurobehavioral function
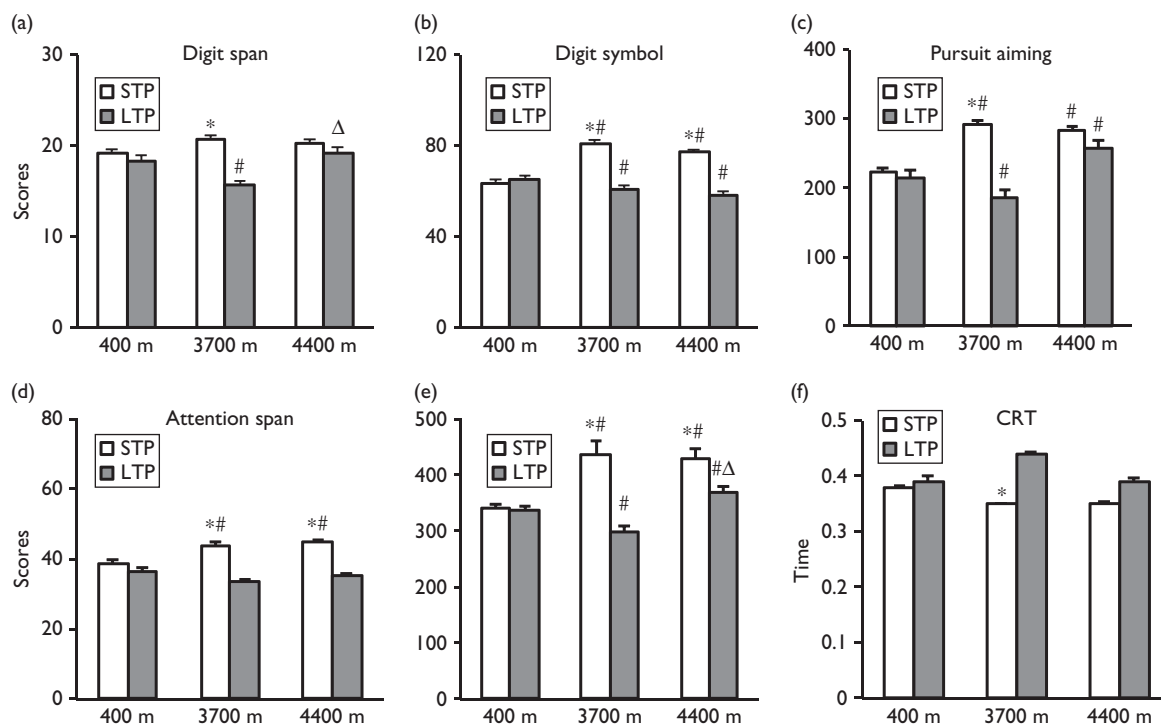
Fig. 1
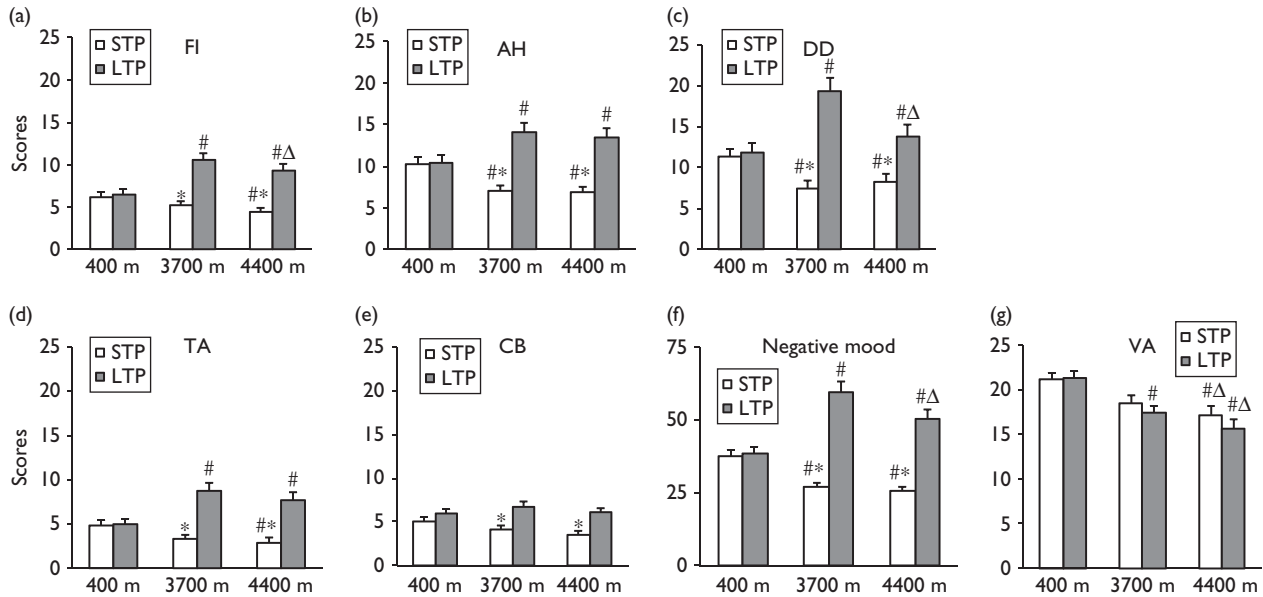
Mood states in STP and LTP groups. The parameters of negative mood states and positive mood states were assessed before HA pre-exposure (400 m), at the end of pre-exposure (3700 m), and on the 10th day of higher altitude exposure (4400 m) in both groups. The scores of fatigue-inertia (FI) (a), anger-hostility (AH) (b), depression-dejection (DD) (c), tension-anxiety (TA) (d), confusion-bewilderment (CB) (e), total negative mood states (f), and positive mood parameter vigor-activity (VA) (g) in the STP and LTP groups are presented as mean ± SEM. HA, high altitude; LTP, long-term HA pre-exposure; STP, short-term HA pre-exposure. *$P < 0.05$; #$P < 0.05$; Δ$P < 0.05$.

at HA, participants were subjected to a 4-day pre-exposure (STP group) or a 3-month pre-exposure (LTP group) at 3700 m before their move to 4400 m altitude. Participants from the two groups had similar demographic characteristics in terms of age, education, smoking and drinking rates, BMI, blood pressure, and heart rate (Table 1). Both groups had similar scores of negative and positive mood states at 400 m before their pre-exposure to HA at 3700 m (Fig. 1a–g). We then evaluated the scores of mood states and found that participants in the LTP group had significantly higher scores of negative mood including FI (Fig. 1a), AH (Fig. 1b), DD (Fig. 1c), TA (Fig. 1d), and CB (Fig. 1e) after HA pre-exposure and on the 10th day of exposure at 4400 m altitude in comparison with the baseline scores at 400 m. In contrast to the LTP group, participants from the STP group had lower scores of negative mood states at both 3700 and 4400 m altitudes (Fig. 1a–e) compared with the baseline scores. The overall scores of negative mood state at 3700 and 4400 m in the STP group decreased significantly in comparison with those in the LTP group (Fig. 1f). Among all the parameters of negative mood states, the DD score was the highest in both groups (Fig. 1c). Evaluation of positive mood state showed that both groups had lower scores at 3700 and 4400 m than at 400 m (Fig. 1g). However, the STP group had a significantly higher score of VA at 4400 m in comparison with the LTP group (Fig. 1g).

Short-term HA pre-exposure enhanced cognitive performance

To examine the consequent benefit of a 4-day versus a 3-month HA pre-exposure at 3700 m on cognitive performance after ascending to a HA at 4400 m, we assessed the scores of the digit span (presented as short-term auditory memory ability), digit symbol (presented as sensorimotor ability), pursuit aiming (presented as movement stability), attention span (presented as attention ability), and the CRT (presented as reaction ability) at the three altitudes (400, 3700, and 4400 m). There was no difference in the baseline scores of the five parameters at 400 m between the STP and LTP groups (Fig. 2a–d). However, participants in the LTP group had significantly lower scores in digit symbol, pursuit aiming, and attention span after pre-exposure to 3700 m and on the 10th day of 4400 m, in comparison with STP group (Fig. 2b–d). Interestingly, we only observed a significantly lower score in digit span at 3700 m, but not at 4400 m in the LTP group (Fig. 2a). On adding the scores of the four parameters together, STP significantly increased the total scores and enhanced participants' cognitive performance at both 3700 and 4400 m altitudes in comparison with LTP (Fig. 2e). Assessment of CRT also showed that the STP group had significantly lower values of CRT at 3700 and 4400 m in comparison with the LTP group (Fig. 2f).

Fig. 2

Cognitive performance in STP and LTP groups. The parameters of cognitive performance were assessed before HA pre-exposure (400 m), at the end of pre-exposure (3700 m), and on the 10th day of higher altitude exposure (4400 m) in both groups. The scores of digit span (a), digit symbol (b), pursuit aiming (c), attention span (d), the above four parameters (e), and the duration of complex reaction time (CRT) in both STP and LTP groups (f), are presented as mean ± SEM. HA, high altitude; LTP, long-term HA pre-exposure; STP, short-term HA pre-exposure. *$P < 0.05$; #$P < 0.05$; Δ$P < 0.05$.

Short-term HA pre-exposure prevented AMS

AMS is the major consequence of HA exposure, and is a key factor affecting the completion of medical and military tasks in an HA environment. To examine the efficacy of STP in preventing AMS, we assessed both the incidence and the score of AMS in the two groups. Evaluation showed that both groups had significantly increased incidences of AMS at both 3700 and 4400 m altitudes compared with the those at 400 m. However, there was a significant decrease in AMS incidence at 4400 m in the STP group compared with the LTP group (Fig. 3a). We also found that AMS incidence at 4400 m in the LTP group was lower than that at 3700 m. However, there was no difference in AMS incidence at 3700 m between the two groups (Fig. 3a). We further measured AMS scores and found that the STP group had significantly lower scores of AMS at both 3700 and 4400 m in comparison with the LTP group (Fig. 3b).

Correlation between cognitive performance and mood states at a higher altitude

The change in mood states exerts effects on cognitive performance. We further analyzed the correlation between cognitive performance and mood states in both
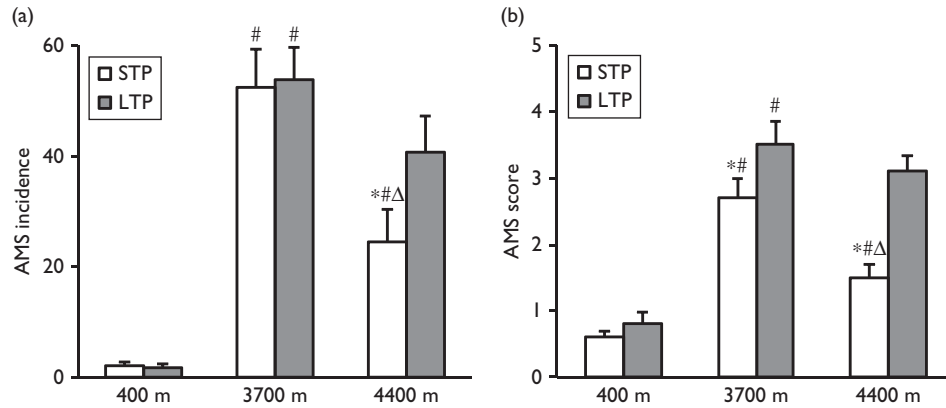
STP and LTP groups on exposure to 4400 m altitude. Statistical analyses showed that the digit symbol was correlated positively to AH ($r = 0.274$, $P = 0.041$) and pursuit aiming was correlated positively to VA ($r = 0.314$ $P = 0.019$) in the LTP group. In the STP group, CRT was correlated positively to FI ($r = 0.395$, $P = 0.008$); digit span was correlated positively to FI ($r = 0.336$, $P = 0.026$); attention span was correlated positively to FI ($r = 0.414$, $P = 0.005$); and pursuit aiming was correlated positively to AH ($r = 0.344$, $P = 0.024$). We did not find any correlation among the other parameters between cognitive performance and mood states in both groups.

Discussion

In this study, we showed that a 4-day STP at 3700 m exerted more benefit toward improving human mood states and cognitive performance, and reducing AMS incidence and severity on exposure to a HA at 4400 m. To our knowledge, this is the first report on the effect of the duration of HA pre-exposure, that is STP versus LTP, on human neurobehavioral ability.

HA exposure at more than 3000 m during military training and operation, recreational, industrial settings, or emergency medical assistance often affects the human

Fig. 3

Acute mountain sickness in STP and LTP groups. The incidence and score of acute mountain sickness (AMS) calculated before HA pre-exposure (400 m), at the end of pre-exposure (3700 m), and on the 10th day of higher altitude exposure (4400 m) in both groups. The incidence (a) and the score (b) in both STP and LTP groups are presented as mean ± SEM. HA, high altitude; LTP, long-term HA pre-exposure; STP, short-term HA pre-exposure. *$P < 0.05$; #$P < 0.05$; Δ$P < 0.05$.

brain and impairs neurobehavioral abilities because of the reduced atmospheric pressure, hypoxia, and consequent hypoxemia [16,18,27,28]. It has been reported that hypoxemia elicits various neurohormonal and hemodynamic responses, which ultimately lead to increased cerebral blood flow and altered permeability of the blood–brain barrier, affecting neurobehavioral parameters [29–31]. HA exposure alters most mood factors for instance fatigue, friendliness, hostility, sleepiness, dizziness, depression, anxiety, confusion, tension, anger, and vigor [32], and has been shown to increase negative mood states [33,34]. Prolonged HA pre-exposure also impairs cognitive performance [18]. In our previous study, we showed that after 6 months of HA pre-exposure, the incidence of anxiety varied from 11.10 to 15.00%, slowly increasing with HA [17]. Another study showed that anxiety decreased significantly after the expedition rather than either before or during the climb [35]. In this study, we observed that a 3-month pre-exposure (LTP group) at 3700 m increased negative mood states; however, after exposure to a HA, negative mood states decreased, whereas most cognitive performances in the STP group were better than those in the LTP group upon exposure to a HA at 4400 m. Interestingly, we also found that there were no significant changes in cognitive performance and mood states between the end of pre-exposure at 3700 m and the 10th day at 4400 m in the STP group. Among all the negative mood state factors, DD had the highest score at both 3700 and 4400 m in the LTP group, which could be related to the stress of human beings reacting to the HA environment. It might also be related to their duty in military as the rates of depression are often higher among military personnel than in the general population [36,37]. However, the specific mechanism that underlines the rapid increase in depression after HA exposure remains unclear.

HA exposure exerts effects on neural activity in the human brain. Neuroimaging showed that long-term HA exposure modified the inferior and middle frontal gyrus and the anterior cingulate cortex [38,39], and affected the response-inhibition processing speed in the conflict-monitoring stage and the neural activity in the matching step of information processing and attentional resources with larger N2 and smaller P3 amplitudes [40]. In terms of attention ability, we indeed found that a 3-month HA pre-exposure reduced the attention span markedly compared with a 4-day pre-exposure, suggesting the possible mechanism by which STP could lead to better benefits than LTP to improve human neurocognitive activity by increasing the attention span when the participants moved in a HA area at 4400 m.

Several investigations have reported the influence of mood state on cognitive performance after HA exposure [41–43], in which they have used simulated climbing and a limited sample size. Using a large number of participants, we found that LTP increased negative mood states and decreased attention ability; however, in contrast with earlier findings [42], we noted that reaction ability was not correlated with mood state. Furthermore, cognitive performance in the LTP was more susceptible to negative mood states (in particular depression) than that in the STP.

Together, our findings suggest that the duration of HA pre-exposure for minimizing the impaired cognitive performance as well as mood states is not necessarily longer and 4-day STP likely has a superior effect in improving human neurobehavioral functions once exposed to a HA.

Conclusion

This study, with large samples, presents important field study evidence that a 4-day STP (at 3700 m) could minimize the adverse effect of HA exposure (at 4400 m) on human neurobehavioral abilities including cognitive performance and mood states, and could reduce the incidence and severity of AMS caused by HA exposure. Our results are not only highly relevant as a guide for the training of military task forces, medical staff, and climbers at altitudes above 4400 m, but also offer a more practical approach to utilize a 4-day STP at 3700 m to promote the medical mission and emergency military support at altitudes above 4400 m.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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