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Long-Term Exposure to High Altitude Affects Voluntary Spatial Attention at Early and Late Processing Stages

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The neurocognitive basis of the effect of long-term high altitude exposure on voluntary attention is unclear. Using event related potentials, the high altitude group (people born in low altitude but who had lived at high altitude for 3 years) and the low altitude group (living in low altitude only) were investigated using a voluntary spatial attention discrimination task under high and low perceptual load conditions. The high altitude group responded slower than the low altitude group, while bilateral N1 activity was found only in the high altitude group. The P3 amplitude was smaller in the high altitude compared to the low altitude group only under high perceptual load. These results suggest that long-term exposure to high altitudes causes hemispheric compensation during discrimination processes at early processing stages and reduces attentional resources at late processing stages. In addition, the effect of altitude during the late stage is affected by perceptual load.

More than 140 million people live permanently at high altitudes (>2,500 m above sea level) in North, Central, and South America, East Africa, and Asia¹. As of 2006, approximately 12 million people live permanently on the Qinghai-Tibetan Plateau, and 71.14% of them live between 2,500 to 4,500 m. In addition, hundreds of thousands of people travel from lowland China to the Tibetan plateau every year; about 6 million Han lowland immigrants now live there permanently^{2,3}. The largest and most important impact of living in a high altitude is hypoxia, which is caused by a reduction of oxygen in the air, and affects cognition. Sustained exposure to high altitude leads to cognitive decrement, such as impairment in attention, memory, judgment, and emotion⁴. Research has demonstrated that cognitive impairment due to altitude starts at 2,500 m above sea level⁵⁻⁷, because brain vulnerability to hypoxia increases beginning at 2,500 m⁸.

Spatial attention may be particularly affected by high altitude exposure. First, the attentional impairment caused by exposure to high altitudes has been found in behavioral tests of visual attention (e.g., the digit symbol substitution test and visual search task)^{9,10}, with slowed reaction times at higher altitudes. Second, previous studies have provided neuroimaging and electrophysiological evidence of the impact of high altitude exposure on the human brain¹¹⁻¹³. In the neuroimaging study, brain areas related to attention processing—including the occipital lobe, parietal lobe, sensory-perceptual regions and frontoparietal attentional networks—were found to be affected by high altitude exposure^{13,14}. In the electrophysiological study, the parietal distributed P3, which is crucially involved in maintaining attention, was the event-related potential (ERP) component most significantly affected by hypoxia^{11,15}. Specifically, smaller and later P3 component responses have been reported for participants at high altitude than in those at the low altitudes, suggesting that cognitive abilities are sensitive to high altitude^{11,16,17}. Third, based on the influence of altitude on the occipital and parietal cortices, the so-called “where pathway” could be affected, indicating that spatial attention abilities are influenced by high altitude exposure.

Spatial attention is manipulated by precueing the location where a target stimulus is likely to appear. Directing visual attention to a cued location facilitates information processing at the attended location, typically leading to faster and more accurate responses^{18,19}. For P1 and N1 potentials, which are distributed throughout the occipital lobe²⁰⁻²² and are enhanced by spatial attention, this phenomenon has been interpreted using the theory of sensory gain control hypothesis²¹ and the maximum of N1 amplitude is located in the right occipital area^{23,24}. The amplitude of the parietally distributed P3 (P3b) component depends on the amount of resources available to process a stimulus^{22,25}. Larger P3 amplitudes were elicited by targets in invalid trials than in valid trials with



informative peripheral cues in long cue-target stimulus onset asynchrony (SOA) tasks. This increased P3 amplitude for invalid trials is most likely due to the decreased probability of the target appearing, or the participant's greater expectation for the target to appear in a certain location^{26,27}. In addition, the C1 component, which is thought to be generated within the primary visual or striate cortex, is attention sensitive under certain conditions and decreases in response to attended stimuli²⁸.

Task difficulty affects the relationship between high altitude and attention impairment, with difficult tasks resulting in a more obvious altitude effect^{7,29}. For instance, Bonnon et al.²⁹ found a greater discrepancy in performance between low and high altitude groups in a difficult compared with an easy task, indicating a greater decline in attention at high altitudes with the complex task. However, to our knowledge, there was no specific ERP evidence of spatial attention impairment related to task difficulty in the high altitude group. Other studies have suggested a neural correlate for the effect of perceptual load on visuospatial attention. Fu et al.²⁸ used a visuo-spatial attention task to examine the interactive effects of perceptual load on ERPs related to visuospatial attention. Perceptual load was manipulated by varying the demand during a figure-ground segregation task. The difference between high and low perceptual load conditions was the complexity of the figure contrasted with the background. The results showed that perceptual load significantly affected visuospatial attention for N1, suggesting that perceptual load interacts with attention at the discrimination stage, as indexed by the N1 component. The P3 component is also sensitive to factors that can affect subjects' performance, with a larger P3 in the difficult condition, which suggests that the P3 amplitude reflects task difficulty.

Despite the known impact of altitude on both attentional ability and visuospatial attention networks, spatial attention has not been directly tested on those living at high altitudes. In the current study, we used a visual attention task manipulating "perceptual load" as used in the study by Fu et al.²⁸. This investigation is the first to apply such a test in high altitude regions.

Additionally, the subjects in our research were more suitable for the study of high altitude than were those used in previous investigations. Most prior research examining cognitive impairment in high altitude subjects focused on either local residents living at high altitudes^{3,30} or people with acute exposure to high altitudes^{11,17,31}. However, the effects of cognitive impairment on high altitude residents typically can not be extrapolated to other populations, because the residents (e.g., native Tibetans) are different from low-altitude residents in terms of genetics and other physiological features^{3,32}. Furthermore, acute and chronic exposure to high altitudes may affect cognition differently, as demonstrated through physiological adaptations to altitude with different immediate and long term effects on ventilatory rate, heart rate and hematocrit³³. Moreover, these physiological changes may also subsequently affect cognition³⁴. To our knowledge, there has been no prior research examining individuals who were born and raised in a low-altitude area, but then relocated to a high-altitude environment for a relatively long period. As immig-

ration and relocation trends continue to grow, with more individuals moving for work, travel, or educational reasons, the study of cognitive impairment due to high altitude hypoxia in relocated groups is increasingly important. Therefore, studying this population will help aid our understanding of the effects of long-term high altitude exposure on cognition.

In the present study, we investigated whether healthy young people who were born and raised in low altitudes, but who were then exposed to chronic hypoxia for three years at high altitudes, showed impairment in a visuospatial attention task; if so, we wanted to know how these attentional impairments were affected by perceptual load. The C1, P1, and N1 components were used as indices of early attentional allocation, whereas the P3 was used as an index of late attention allocation. First, we hypothesized there would be a significant effect of attention on behavioral and ERP responses in both high and low altitude groups. Specifically, we anticipated participants would have quicker and more accurate responses in valid relative to invalid trials, and that P1 and N1 amplitudes would be larger in valid compared with invalid trials. In contrast, C1 and P3 amplitudes would be smaller in valid trials relative to invalid ones. Second, because the parietal and occipital cortices are influenced by high altitude exposure^{13,35}, we predicted that individuals at high altitudes would be significantly affected in the early and late processing stages of spatial attention. At the early stage, based on the impact of high altitude on the occipital cortex, and given the relationship between N1 and the occipital cortex^{13,22}, we anticipated seeing group differences in N1 component amplitude. At the late stage of processing, we expected to see group differences in the P3 component, with a smaller P3 amplitude in the high altitude group^{6,11,15,17}. Finally, given that task difficulty influences the effect of altitude on attentional performance, we hypothesized there would be a significant interaction effect of perceptual load and altitude on ERP components^{11,36}.

Results

Behavioral results. The low altitude group reacted faster on the task than the high altitude group [580.72 ± 56.00 ms vs. 622.08 ± 77.54 ms; $F(1, 34) = 5.73, p = 0.028$] (Table 1). The cue validity effect was significant, with all participants reacting more quickly [579.64 ± 63.60 ms vs. 623.16 ± 69.95 ms; $F(1, 34) = 100.13, p < 0.0001$] and accurately [96.46 ± 2.61% vs. 92.16 ± 4.60%; $F(1, 34) = 47.96, p < 0.0001$] (Table 1) on valid than invalid cues. Participants also responded faster [525.78 ± 55.47 ms vs. 677.02 ± 78.08 ms; $F(1, 34) = 250.35, p < 0.0001$] and more accurately [97.93 ± 1.90% vs. 90.69 ± 5.31%; $F(1, 34) = 109.96, p < 0.0001$] (Table 1), in the low perceptual load condition than in the high perceptual load condition. The altitude × perceptual load interaction was significant for accuracy rate [$F(1, 34) = 6.89, p = 0.018$] (Table 1); the high altitude group reacted less accurately than the low altitude group only in the high perceptual load condition [88.91 ± 5.81% vs. 92.46 ± 4.80%; $F(1, 17) = 4.63, p = 0.046$] (Fig. 1). No other significant main effects or interactions were found for behavioral results.

Table 1 | The important main effects and interactions on behavioral and ERP components. ACC, accuracy rate; RT, reaction time; Amp., amplitude; V, cue validity effect; A, altitude effect; PL, perceptual load; hemi., hemisphere; D, distance from the midline

Variable	ACC		RT		N1 Amp.		P3 Amp.	
	F	P	F	P	F	P	F	P
V	47.96	<0.0001	100.13	<0.0001	18.00	<0.001	-	-
A	-	-	5.73	0.028	-	-	4.12	0.05
PL	109.96	<0.0001	250.35	<0.0001	31.24	<0.0001	36.46	<0.0001
A × PL	6.89	0.018	-	-	-	-	4.21	0.048
A × hemi.	-	-	-	-	5.02	0.032	-	-
A × V × hemi. × D	-	-	-	-	5.79	0.02	-	-



ERP results. C1. For the C1 amplitude, the main effect of altitude was significant [$-2.83 \pm 0.29 \mu\text{V}$ vs. $-2.03 \pm 0.27 \mu\text{V}$; $F(1, 34) = 7.29$, $p < 0.05$], indicating that C1 amplitude was larger in the high altitude group than in the low altitude group. The main effect of validity was significant [$-2.57 \pm 0.26 \mu\text{V}$ vs. $-2.29 \pm 0.31 \mu\text{V}$; $F(1, 34) = 4.87$, $p < 0.05$], with C1 in the invalid trials being larger than in the valid trials. No other main effects or interactions were significant.

P1. The main effect of perceptual load was significant [$2.80 \pm 0.49 \mu\text{V}$ vs. $2.49 \pm 0.46 \mu\text{V}$; $F(1, 34) = 10.96$, $p = 0.002$], indicating that P1 amplitude was greater in the high perceptual load condition than in the low perceptual load condition. The main effect of validity was also significant [$3.22 \pm 0.46 \mu\text{V}$ vs. $2.07 \pm 0.49 \mu\text{V}$; $F(1, 34) = 19.71$, $p < 0.001$], with a larger P1 in the valid than in the invalid trials. No other main effects were significant. The validity \times visual field \times hemisphere interaction was significant [$F(1, 34) = 27.62$, $p < 0.001$]. To analyze the interaction, a simple effect test was carried out on the combined visual field/hemisphere data (ipsilateral vs. contralateral), where valid trials elicited a larger P1 at contralateral temporal sites [$3.06 \pm 0.51 \mu\text{V}$ vs. $1.07 \pm 0.44 \mu\text{V}$; $F(1, 35) = 33.37$, $p < 0.001$].

For the latency of the P1 component, the main effects of validity [116.22 ± 2.80 ms vs. 128.80 ± 3.13 ms; $F(1, 34) = 75.60$, $p < 0.0001$], and perceptual load [120.67 ± 2.83 ms vs. 124.35 ± 3.10 ms; $F(1, 34) = 10.67$, $p = 0.002$], were significant. No other main effects were significant. The validity \times visual field \times hemisphere interaction was also significant [$F(1, 34) = 15.15$, $p < 0.001$]. Moreover, the invalid trials elicited a longer P1 latency at ipsilateral temporal sites [139.32 ± 3.29 ms vs. 122.63 ± 3.09 ms; $F(1, 35) = 89.58$, $p < 0.0001$].

N1. The main effect of perceptual load was significant [$-2.95 \pm 0.58 \mu\text{V}$ vs. $-2.21 \pm 0.50 \mu\text{V}$; $F(1, 34) = 31.24$, $p < 0.0001$] (Table 1), with N1 in the high perceptual load condition being more negative than in the low perceptual load condition. The main effect of validity was also significant [$-3.10 \pm 0.57 \mu\text{V}$ vs. $-2.06 \pm 0.52 \mu\text{V}$; $F(1, 34) = 18.00$, $p < 0.001$] (Table 1), with N1 amplitude being greater in the valid cue trials than the invalid trials. Meanwhile, the interaction between perceptual load and validity was significant [$F(1, 34) = 28.65$, $p < 0.001$]. Furthermore, valid trials elicited larger N1 than invalid trials in both high [$-3.76 \pm 0.62 \mu\text{V}$ vs. $-2.13 \pm 0.54 \mu\text{V}$; $F(1, 35) = 27.76$, $p < 0.001$] and low perceptual load conditions [$-2.43 \pm 0.52 \mu\text{V}$ vs. $-1.98 \pm 0.49 \mu\text{V}$; $F(1, 35) = 4.58$, $p = 0.039$]. In addition, the interaction between hemisphere and altitude was also significant, [$F(1, 34) = 5.02$, $p = 0.032$] (Table 1), with a larger N1 amplitude in the right hemisphere than in the left hemisphere in low altitude group [$-3.34 \pm 0.62 \mu\text{V}$ vs.

$-1.47 \pm 0.51 \mu\text{V}$; $F(1, 17) = 8.26$, $p = 0.011$] (Fig. 2a). The cue validity \times hemisphere \times distance from the midline \times altitude group interaction was significant [$F(1, 34) = 5.79$, $p = 0.022$] (Table 1). Moreover, altitude effect was marginally significant in the valid cue trials at the electrode codes far from the midline position on the left hemisphere, with larger N1 amplitude in the high altitude group than in low altitude group [$-3.11 \pm 0.45 \mu\text{V}$ vs. $-1.83 \pm 0.47 \mu\text{V}$; $F(1, 34) = 3.68$, $p = 0.063$]. No other main effects or interactions were significant. Figure 2b further revealed the dynamic topography within the N1 time window, demonstrating that the hemisphere asymmetry was only found in low altitude group, while the left and right electrode sides were both activated in the high altitude group.

For the latency of N1, the interaction between perceptual load and validity was significant [$F(1, 34) = 6.95$, $p = 0.013$]. Further analysis revealed that only in the high perceptual load conditions invalid trials elicited later N1 than the valid trials [165.63 ± 3.47 ms vs. 161.18 ± 2.93 ms; $F(1, 35) = 5.69$, $p = 0.023$]. The perceptual load \times validity \times hemisphere \times visual field interaction was significant [$F(1, 34) = 6.90$, $p = 0.013$]. To analyze this interaction, a simple effect test was carried out on the combined visual field/hemisphere data (ipsilateral vs. contralateral). In the high perceptual load condition, compared to the valid trials, the latency of N1 elicited by the targets in the invalid cue trials was later at ipsilateral sites [173.51 ± 3.94 ms vs. 165.20 ± 3.54 ms; $F(1, 35) = 10.84$, $p = 0.002$]. No other main effects or interactions were significant.

P3. For the P3 latency, no effect was significant. For the P3 amplitude, the main effect of altitude was significant [$6.19 \pm 0.79 \mu\text{V}$ vs. $8.15 \pm 0.68 \mu\text{V}$; $F(1, 34) = 4.12$, $p = 0.05$] (Table 1), indicating that P3 amplitude was smaller in the high altitude group than in the low altitude group (Fig. 3). The main effect of perceptual load was also significant [$8.15 \pm 0.74 \mu\text{V}$ vs. $6.20 \pm 0.73 \mu\text{V}$; $F(1, 34) = 36.46$, $p < 0.0001$] (Table 1), with P3 in the low perceptual load condition being more positive than in the high perceptual load condition. Moreover, the main effect of validity was also significant [$7.38 \pm 0.73 \mu\text{V}$ vs. $6.96 \pm 0.74 \mu\text{V}$; $F(1, 34) = 4.90$, $p = 0.034$], with P3 being larger in the invalid trials than the valid trials. Additionally, the interaction between perceptual load and altitude was significant [$F(1, 34) = 4.21$, $p = 0.048$] (Table 1). Further analysis showed that the difference between low altitude group and high altitude group was only significant in the high perceptual load condition, while P3 amplitude in the high altitude group was smaller than that in the low altitude group [$4.89 \pm 0.77 \mu\text{V}$ vs. $7.51 \pm 0.69 \mu\text{V}$; $F(1, 34) = 6.64$, $p = 0.014$] (Fig. 4). No other significant main effects or interactions were found.

Discussion

Our study investigated the cognitive impact of long-term exposure to high altitude on healthy young people during a visual-spatial attention task under high and low perceptual load conditions. The results provide insight into the neural mechanisms responsible for modulation of early and late stage of spatial attention after long-term exposure to high altitude, and these findings supported confirmed several of our hypotheses. First, consistent with previous studies^{18,28,37,38}, there was significant effect of attention on behavioral and ERP responses, with participants responding more quickly and accurately for valid compared with invalid cues, indicating that the cue did indeed attract attention to the cued location^{18,39}. The increased C1 amplitude seen for invalid trials compared with valid trials maybe because participants had to process the distractors at a very early stage in this task²⁸. The larger P1 and N1 amplitudes in valid trials compared with invalid ones can be interpreted by referring to the sensory gain control theory of visual attention^{37,40,41}. The increased P3 amplitude for invalid relative to valid trials confirmed that P3 remains an effective index of fundamental attention-related operations^{38,42}. Second, the altitude effect was significant for beha-

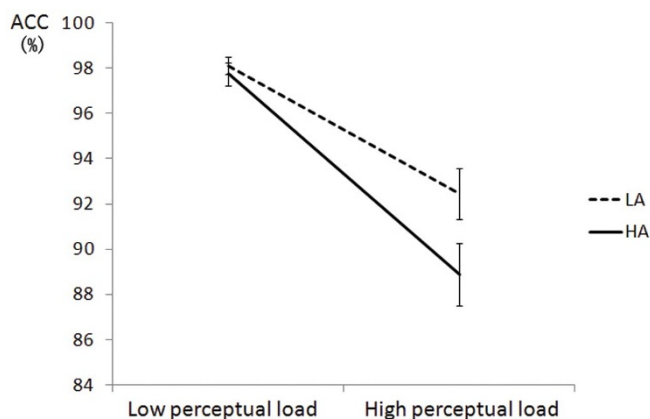


Figure 1 | Behavioral result. Mean accuracy rate (ACC) and standard error (percent) for the low altitude group (LA) and high altitude group (HA) of subjects under both the low and high perceptual load conditions.

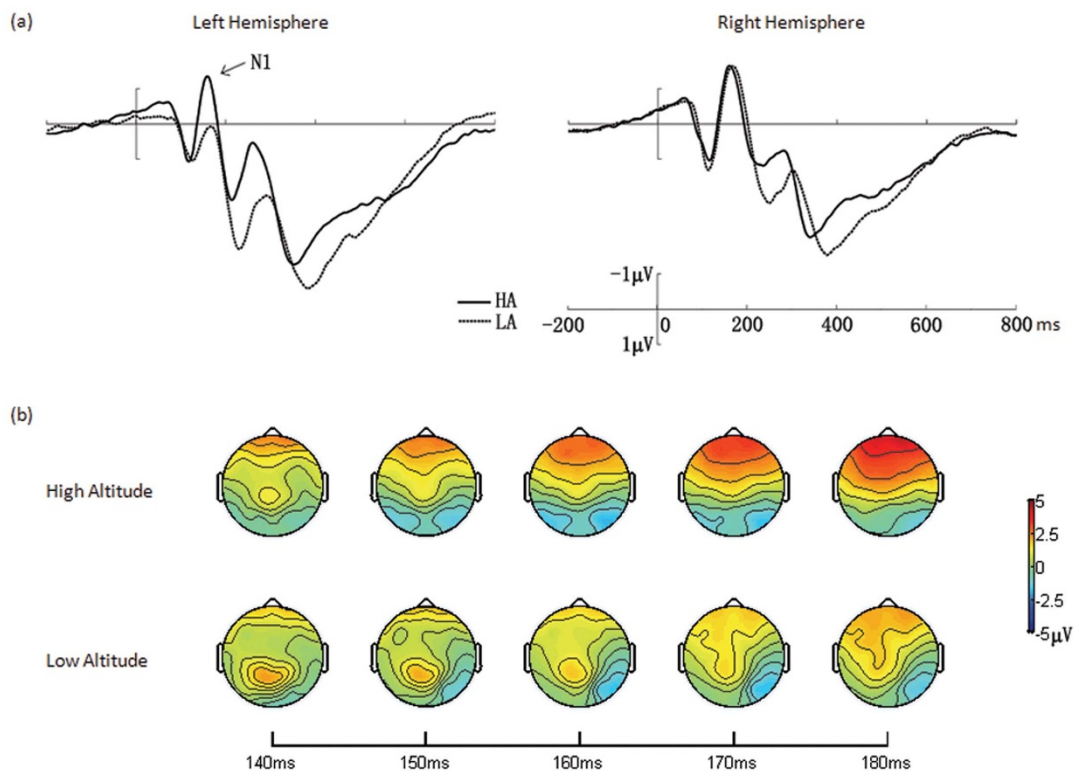


Figure 2 | (a) Grand average of ERP elicited by the low altitude group (LA, dotted lines) and high altitude group (HA, solid lines) at the posterior sites. Data were averaged across the low and high perceptual load conditions, valid and invalid cue trials, electro sites (P5, P6, P7, P8, PO5, PO6, PO7, PO8), and visual fields. (b) Sequential topographic voltage maps of N1 component as a function of altitude (high and low). The topographical maps were generated every 10 ms from 140 ms to 180 ms. Data were averaged across 18 participants for each group.

vioral and ERP data, as demonstrated by slower response times in the high altitude compared with the low altitude group. At the early processing stage, a hemispheric difference in N1 amplitude was found between the two altitude groups, while at the late processing stage the amplitude of P3 was smaller in the high altitude than in the low altitude group. Third, the interaction between altitude and perceptual load was found for both behavioral data and the P3 component, with the high altitude group responding less accurately and having a smaller P3 than the low altitude group in the high perceptual load condition.

The major finding of the present study was that spatial attention processing was significantly affected by altitude, which was evident in both behavioral and ERP results. For the behavior result, the high altitude group reacted slower than the low altitude group under all conditions. Consistent with other studies, the reaction time delay in the high altitude group might reflect altered sensoriperceptual processing^{7,43,44}.

For the ERP results, at the early processing stage, we found hemispheric differences between the altitude groups on the N1 component. The altitude effect was marginally significant in valid cue trials at the P7 and PO7 sites in the left hemisphere, with a larger N1 in the high altitude than in the low altitude group. According to previous research, the N1 is related to the operation of a limited-capacity discrimination mechanism, which in turn reflects the operation of a general-purpose visual discrimination mechanism²². Our results indicate that this visual discrimination mechanism may be affected by altitude. For example, in the low altitude group, the N1 amplitude in the right hemisphere was larger than that in the left hemisphere, while in the high altitude group there was no difference between the two hemispheres. The N1 amplitude in the right hemisphere was also as large in the high altitude group as the low altitude group. In the N1 time window, only the right posterior sites were active in the low altitude group, while bilateral posterior sites were active in the high altitude group (Figure 2b). This hemispheric asymmetry of the N1

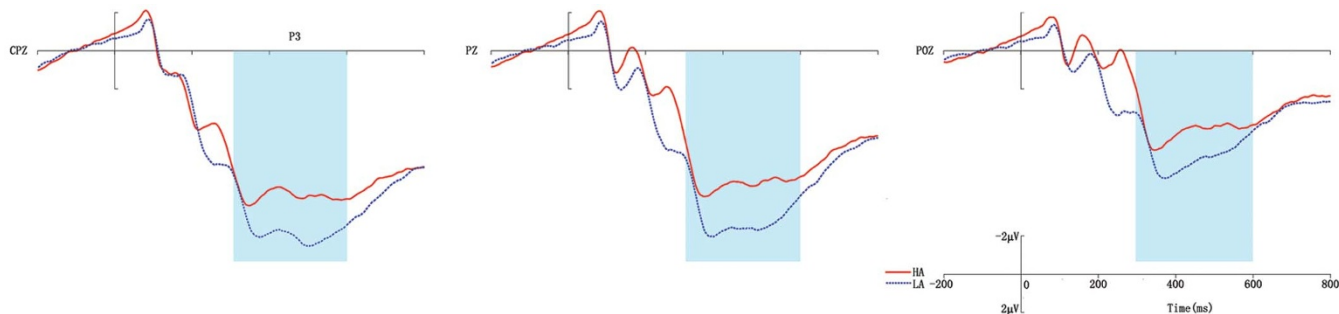


Figure 3 | Grand average of ERP elicited by the low altitude group (LA, dotted lines) and high altitude group (HA, solid lines) at the central sites. Data were averaged across the low and high perceptual load conditions as well as valid and invalid cue trials.

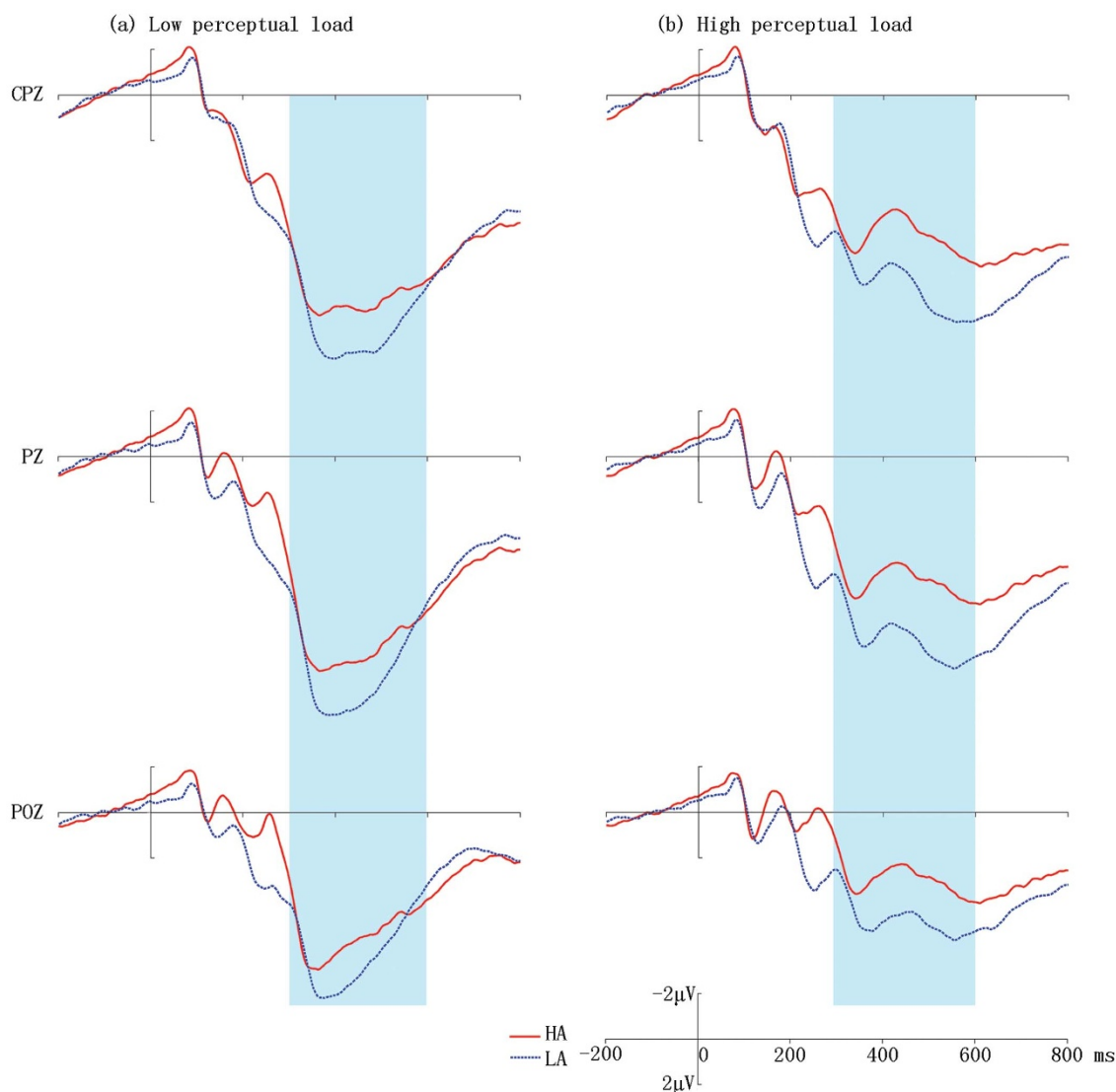


Figure 4 | Grand average of ERP elicited by the low altitude group (LA, dotted lines) and high altitude group (HA, solid lines) under the low (a) and high (b) perceptual load conditions at the central sites. Data were averaged across the valid and invalid cue trials.

amplitude in the low altitude group was similar to results from previous studies demonstrating the dominance of the right hemisphere in visual-spatial attention tasks^{45,46}. Notably, the bilateral activity in the high altitude group may indicate a compensatory mechanism in the left hemisphere during the discrimination stage. As there was an increased demand on target processing for the high altitude group, it is possible that these participants had to maintain a higher activation level, expending more effort than the low altitude group to accomplish the same task.

This is a novel finding of the present study, as previous research suggested that increased altitude did not affect the earlier N1 component, only influencing the later P3 component^{11,15}. There are two possible explanations for the different N1 findings between the present study and prior investigations. First, the unchanging N1 in previous tasks may be due to the participants' acute exposure to hypoxia or simulated hypoxia conditions. Using functional magnetic resonance imaging (fMRI) technique, Yan et al.¹³ found decreased activation in the occipital cortex in Han residents who were born and raised in a high altitude location. The N1 component that reflected the operation of discrimination processing in voluntary attention had highly reliable and focused activity in the occipital-temporal cortex⁴⁷. Therefore, based on the findings of Yan et al.¹³ and Hopf et al.⁴⁷, the impact of high altitude exposure on the occipital region

might account, to some extent, for the changing N1. Second, the unchanging N1 between groups in previous studies may also be because the tasks they adopted did not require significant discrimination processing. In our study, the high and low perceptual load stimuli were presented randomly, requiring participants to spend more effort on discriminating between stimuli, which potentially resulted in the group differences in N1 amplitude. We also found a group difference in C1 amplitude, which suggests that the modulation of high altitude may start from a very early processing stage.

We also observed a smaller P3 in the high altitude group than in the low altitude group. The P3 component is regarded as an index of brain activity underlying the mental representation induced by incoming stimuli, reflecting sensory processing as well as the degree of modification^{11,48}. The smaller P3 amplitude in the high altitude group, compared with that in the low altitude group, suggests that the degree of brain activity for current information processing was lower in the high altitude than in the low altitude group. Additionally, a main effect of cue validity was also significant on P3 amplitude in the current study. Based on the results of prior research, the smaller P3 amplitude in the high altitude group might reflect a diminished availability of attentional resources for completing the task, as the attentional capacity of the high altitude group was affected by hypoxia^{15,22,49}. Although P3 latency has been suggested to reflect a slow-

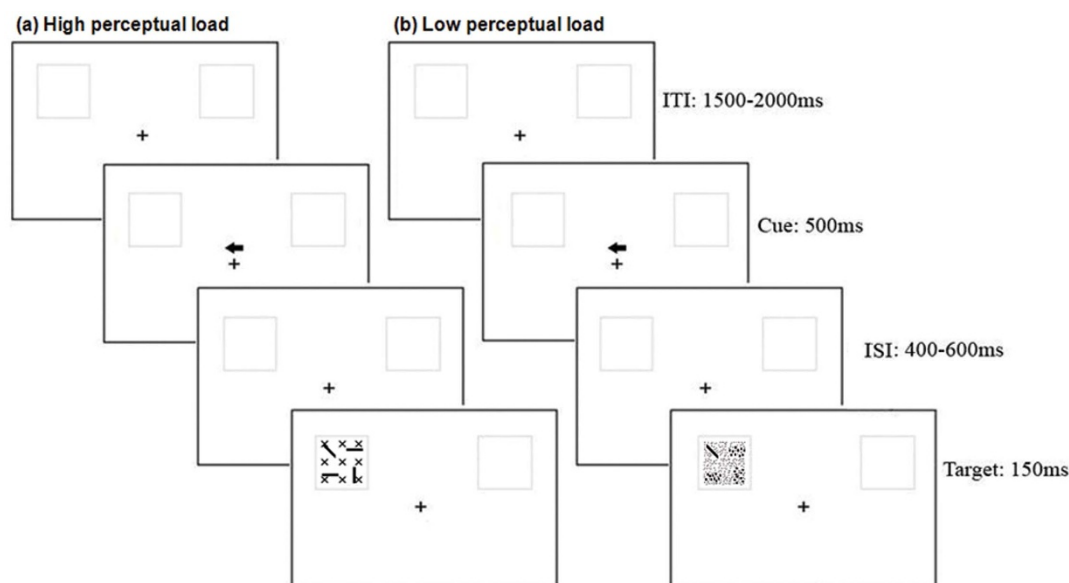


Figure 5 | Materials and procedure. The procedure of the experimental paradigm, valid cue trials under the high perceptual load condition (a), and the low perceptual load condition (b).

ing down of signal processing caused by hypoxia, we did not find group differences in P3 latency, as reported in previous studies^{11,16,17}. One possibility for this discrepancy is adaptation, that is, the relatively long exposure to high altitude in our participants may have adapted them to hypoxia. Thus, the P3 latency change at high altitudes seen in previous studies might depend on how long individuals have lived in a high altitude location^{16,17}. Consistent with this theory, Singh et al.⁶ and Richardson et al.³⁰ found that with longer exposure to high altitude, the P3 latency became more similar to that of people from a low altitude, suggesting there is an adaptation to hypoxia.

The influence of high altitude on attention was affected by perceptual load. For behavioral results, the high altitude group responded less accurately than did the low altitude group in the high perceptual load condition only, suggesting that the high altitude group might suffer from attentional deficits only during more cognitively demanding conditions. For the ERP results, the difference between the altitude groups was also only significant under the high perceptual load condition, with a smaller P3 in the high altitude compared with the low altitude group. Because the P3 component is sensitive to factors that can affect subjects' performance, such as task difficulty, and given that P3 amplitude reflects an evaluation of task difficulty, the greater difficulties experienced by the high altitude group during the high load condition likely reflects a depletion of processing capacity in this group^{11,36,50}. Thus, when greater cognitive resources were needed to complete the high perceptual load task, the differences between the altitude groups became more obvious. The absence of a difference between the two groups under the low perceptual load condition suggests that, when fewer cognitive resources are required, ability is not affected by altitude. Overall, the results suggest that altitude has a significant impact on attention, which is in turn significantly affected by perceptual load, particularly at the late processing stage.

One limitation of our study is that, although attention was influenced by high altitude in people living in Lhasa for three years and participants had acclimated to the high altitude environment, results should still be interpreted cautiously, as living elsewhere may be influenced by other factors (e.g., differences in climate or culture). Further investigations could include immigrants living at high altitudes for a longer period, or studying people who relocate to a low altitude after living at high altitudes for a long time. Additionally, although complete physical adaptation to 3,600 m occurs after 40

days, physical signs (e.g., ventilation rate, heart rate, blood pH) could be included in future studies for additional confirmation of acclimation.

In conclusion, our study demonstrates that altitude alters attentional processing at both early and late stages, as evidenced by its effect on the N1 and P3 components. Moreover, the effect of altitude at the late processing stage is affected by perceptual load. The hemispheric differences between the altitude groups on the N1 component likely reflect the impact of high altitude on attention discrimination processes, suggesting the presence of a compensation mechanism in the high altitude group. The smaller P3 amplitude in the high altitude group suggests that attentional resources available to process stimuli are decreased in this group. Critically, the altitude effect at the late processing stage existed only under the high perceptual load condition. Therefore, long-term exposure to high altitude affects attention, and this effect is modulated by perceptual load.

Methods

Participants. A total of forty young healthy participants were tested and informed consent was obtained from all participants. The experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences. The high altitude group consisted of 20 college students (aged 21–24 years) from Tibet University. The low altitude group included 20 healthy students (aged 20–24 years) from multiple universities in Beijing. Two participants from each group were discarded because of low accuracy rate, frequent eye movements or excessive artifacts in the electroencephalogram (EEG), leaving 18 participants in each group. The eighteen participants in the high altitude group included 9 females and 9 males, aged between 21–24 years old (22.67 ± 0.77 years). They were all born and raised in low altitude environments (883.93 ± 703.38 m), but had lived for 3 years in Lhasa in the Tibetan Plateau at altitudes of 3,650 m, returning to low altitudes for less than 2.53 ± 0.92 months each year. According to previous studies, a permanent and stable acclimatization to 3,600 m is achieved at around 4 weeks, and complete hematocrit adaptation is achieved after 40 days^{33,51,52}. In this regard, three years is adequate time for the human body to adapt to high altitude through long-term acclimatization. The eighteen participants in the low altitude group included 8 females and 10 males, aged between 20–24 years old (21.72 ± 1.12 years). They were all born and raised in low altitude environments (620.67 ± 719.84 m) and had never been to the high altitude location. The groups were matched for education level (15.00 ± 0.00 years for high altitude group, 14.88 ± 0.47 for low altitude group) and had similar scores in the national examinations for college entrance. All participants were from the Han ethnic group, right handed, and had normal or corrected to normal vision.

Stimuli. The stimuli for the visual voluntary attention task were presented via an Intel Core 2 Duo computer. The background of the display consisted of a central fixation cross ($0.66^\circ \times 0.66^\circ$) and two gray square boxes ($3.44^\circ \times 3.44^\circ$) on a white screen, with their center 6.06° lateral to and 2.62° above the fixation cross. In the high



perceptual load condition, the visual search array ($2.78^\circ \times 2.78^\circ$) had four lines: two horizontal (“—”), one vertical (“|”), and one diagonal (the target line, which could be either backward “\” or forward “/”) displayed on a background array of Xs. In the low perceptual load condition, the non-target lines (horizontal and vertical) in the visual search array were cut into ten pieces, and these small pieces were scrambled in their respective quadrant. The background Xs were also cut into small pieces and scrambled around the four regions occupied by the diagonal line and the three ten-piece-distractors. This helped the diagonal line to “pop out” from the surroundings, which made it easier for participants to find the target-diagonal line and reduced perceptual demand for the low load condition. The high-load and low-load search arrays were randomized and presented with equal frequency in the experiment, and all search arrays appeared randomly in the left or right gray square boxes. The diagonal line (backward “\” or forward “/” with equal probability) could appear randomly at any one of the four quadrants of the gray square box. Each trial contained a predictive endogenous cue (75% validity) to prime visual attention. The cue was an arrow ($1.1^\circ \times 1.1^\circ$) presented 0.98° above the fixation cross (Fig. 5). The luminance values of the screen background (24.2 cd/m^2) and the stimuli (0.05 cd/m^2) were the same between the low-load and high-load conditions.

Procedure. Sufficient practice (five minutes for each subject) was provided to make sure that all participants’ accuracy rate could reach more than 80%.

The EEG experiment lasted approximately 1.5 hours, containing 52 blocks in total, each composed of 32 trials. After each block, participants could have a rest, the length of which was under their control. Each trial consisted of the following sequence (Fig. 5). During the test, a fixation cross and two gray boxes were presented continuously on the computer screen. Each trial began with an arrow (representing an endogenous spatial cue) being flashed above the fixation cross, randomly pointing to the left or right side. The arrow cue was displayed for 500 ms, with 75% of the cues being valid and 25% invalid. Next, the visual search array (including the diagonal target line) was presented for 150 ms, with the inter-stimuli interval (ISI) between cue and target varied randomly in the range of 400–600 ms. The inter-trial interval (ITI) was varied randomly between 1500–2000 ms.

After the EEG cap was fitted and prepared, participants were seated in a comfortable armchair about 70 cm in front of the monitor in a dimly lit, electrically isolated room. During the test, they were instructed to sit in a relaxed position, fix their eyes on the cross in the center of the screen, and limit eye blinks and body movements. When the search array appeared on the screen, they were requested to respond to all of the targets as quickly and accurately as possible. When the backward line “\” appeared, they ought to use their right index finger to press the key “J” on the keyboard, and left index finger to press “F” when the forward line “/” appeared. Response time, accuracy, and EEG data were recorded during the whole procedure. Stimulus display and behavioral data acquisition were conducted using E-Prime software (Version 1.1, Psychology Software Tools, Inc., Pittsburgh, PA).

ERP recording. The EEG was recorded from 64 Ag/AgCl electrodes mounted in an elastic cap (Neuroscan Inc.). The physical reference electrode was approximately 2 cm posterior to CZ, and the EEG data were re-referenced to the average of left and right mastoid (M1 and M2). The vertical electrooculogram (VEOG) was recorded with electrodes placed above and below the left eye. The horizontal electrooculogram (HEOG) was monitored by placing two electrodes 10 mm from the outer canthi of both eyes. All inter-electrode impedances were maintained below 5 k Ω . Signals were amplified with a 0.05–100 Hz bandpass filter and digitized at 500 Hz.

Data analysis. Behavioral data were analyzed by means of mixed-model analysis of variance (ANOVA). Reaction times (RTs) were online recorded for all the participants. The accuracy rates and the RTs for correct responses were used for data analysis. The independent variables were cue validity (valid and invalid) and perceptual load (low and high) as within-subject factors, and altitude group (high altitude and low altitude) as between-subject factor for a $2 \times 2 \times 2$ design. Reaction times less than 100 ms or more than 3 standard deviations slower than the participants mean reaction time were excluded prior to data analysis (a total of 984 trials or 1.64% of the data). Ocular artifacts were removed from the EEG signal using a regression procedure implemented using Neuroscan software⁵³. The data were divided into epochs of 1000 ms in length, including a 200 ms interval before the target onset. The EEG data were digitally filtered with a 40 Hz low pass filter offline, and each channel was baseline corrected using the pre-stimulus 200 ms interval. Trials with various artifacts were rejected, with a criterion of $\pm 75 \mu\text{V}$. Only correct response trials were included for average ERP. Trials with response errors, a RT less than 100 ms or more than 3 standard deviations above the participant’s mean reaction time, body movements, or muscle activity were excluded (a total of 4511 trials, or 7.53% of the data). The ERPs were averaged separately for all combinations of task conditions. The target ERPs were averaged separately from the time point of their onset. Peak amplitudes and peak latencies were used for statistical analyses for the C1, P1, and N1 components. The mean amplitude and 50 percent area latency were adopted for P3 components²⁰. The mean latency was defined as the sampling point where a pre-specified fraction (50% in this case) of the total area was reached. For each participant, the combination of the jackknife method and fractional area latency measure produced the onset latencies of the P3 wave. The amended results are reported in line with previous studies^{54,55}. Specifically, The statistical results (F-values and t-values) were corrected using the formulas: $FC = F/(N - 1)$, and $tC = t/(N - 1)$, where N denotes the number of observations in each condition. The time windows for C1, P1, N1, and P3 components were 50–120 ms, 90–160 ms, 150–250 ms, and

300–600 ms, respectively. We selected the specific time windows for each ERP component by visual inspection of ERP grand averages. For electrophysiological data analysis, data were analyzed from electrode exhibiting the largest amplitude waveform of each component of interest. Eight electrode sites (P5, P6, P7, P8, PO5, PO6, PO7 and PO8) were selected for P1 and N1 data analysis. A mixed-model ANOVA was applied to different components. The ANOVA factors for P1 and N1 components included cue validity (two levels: valid and invalid), perceptual load (two levels: low and high), altitude group (two levels: high altitude and low altitude), visual field (two levels: left and right), hemisphere (two levels: left and right), anterior-posterior (two levels: electrode sites in front or back), and the distance from the midline (two levels: electrode sites near or far from the midline). The factors for C1 and P3 components were the same as P1 and N1 without the hemisphere, anterior-posterior, and the distance from the midline factors, and restricted to three central electrodes (CPZ, PZ, and POZ). The Greenhouse–Geisser correction was used to compensate for sphericity violations. Post hoc analyses were conducted to explore interaction effects.

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Author contributions

Y.W., H.M. and S.F. designed research; Y.W., H.M. and P.L. performed research; Y.W. and S.G. analyzed data; S.G. contributed analytic tools; and Y.W., S.F., X.Y. and B.H. wrote the paper.

Additional information

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