A Longitudinal study on the impact of high-altitude hypoxia on perceptual processes

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Abstract

This study aimed to explore the neural mechanism underlying high-altitude (HA) adaptation and deadaptation on perceptual processes in lowlanders. Eighteen healthy lowlanders were administered a facial S1-S2 matching task that included incomplete face (S1) and complete face (S2) photographs, combined with ERP technology. Participants were tested shortly before they went to HA at sea level (Test 1), twenty-five days after entering HA (Test 2), one week (Test 3) and one month (Test 4) after returning to lowlands. Compared with sea level baseline, shorter latencies of P1 and N170 and larger amplitudes of complete face N170 were found in HA. After returning to sea level, compared with HA, the amplitude of the incomplete face P1 was smaller after one week and the complete face was smaller after one month. The right hemisphere N170 amplitude was larger after entering HA and one week after returning to sea level compared to baseline, but it returned to baseline after one month. Taken together, the current findings suggest that HA adaptation increases visual cortex excitation to accelerate perceptual processing. More mental resources are recruited during the configural encoding stage of complete faces after HA exposure. The perceptual processes affected by HA exposure is reversible after returning to sea level, but the low-level processing stage is different between incomplete and complete faces due to neural compensation mechanisms. The configural encoding stage in the right hemisphere is affected by HA exposure and requires more than one week but less than one month to recover to baseline

Introduction

The human brain, especially the cerebral cortex, is extremely sensitive and vulnerable to hypoxia . Oxygen supply is essential to maintaining the normal function of brain's cognitive processes, which can be conceived as a hierarchy of several serial phases, from early sensory-perceptual stages, to higher-order cognitive processes (Mayevsky et al., 1986). Hypoxia, whether environmental or pathological, such as exposure to a hypobaric chamber or living at high altitude (HA), chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), has been found to broadly impact cognitive functions . Among them, HA is an important residential region for human beings. Despite thousands of years of struggle, hypoxia remains a significant public health problem. Extant studies have documented neurologic deficits, cognitive dysfunctions, and brain abnormalities, such as hallucinations under HA conditions , which directly impair people's living quality and work efficiency and thus cannot be ignored. Exposure to HA provides a natural, convenient to observe, low-cost and reproducible model for studying hypoxia in healthy individuals, which not only has guiding significance on plateau activity, but also might provide new insights for understanding hypoxia in clinical settings.

A number of studies have shown that HA exposure exerts a range of deleterious effects on cognitive processes, verbal fluency, cognitive flexibility, executive function, metacognition, etc. (Taylor et al., 2016; Yan, 2014), while others indicating the presence of compensation mechanisms to help maintaining cognitive performances . The inconsistence across studies may be attributed to the cognitive domain being interrogated . Since the human brain is inherently plastic, its functional structure can be reorganized in response to environmental and physiological alterations , those cognitive processes, e.g. higher-order cognitive functions which involve the prefrontal lobe, may employ an adaptive process to compensate for the neurocognitive impairment and thus be less affected by hypoxia . Nonprefrontal lobe functions, such as visual perception processing, reaction time (RT) , perceptive discrimination, and color perception, demonstrated to be more sensitive to hypoxia and are critical for the brain in adaptation to HA (Chen et al., 2016), making it particularly suitable for monitoring hypoxia adaptation of cognitive processes, which may help us understand how the brain acclimates to harsh environments.

Previous studies indicated that brain electrophysiological activity in the visual cortex may explain the alterations in visual cognition . Among all visual inputs, face perception is one of the most developed visual perceptual skills of human beings, and it plays a major role in social interaction, which constitute the perceptual basis for interpersonal communication. Nevertheless, few studies have directly examined the neural processing of face information under HA hypoxia conditions. Perceptual organization refers to the process of integrating fragments of stimuli into a coherent pattern . ERPs are widely used in perceptual organization studies. P1 and N170 are universally recognized as two main face-sensitive brain potentials. The P1 component reflects the low-level processing of face perception . The N170 component is considered to index the perceptual categorization of faces , which reflects high-level face perception and the configural encoding of facial features as well as their integration into a holistic perception . As a crucial cognitive function, perceptual alteration under HA can help advance our understanding of the impact of HA hypoxia on nonprefrontal tasks.

After prolonged HA exposure, the individual experiences a series of physiological and biochemical adaptive responses, e.g., increases in oxygen-carrying hemoglobin levels and ventilation, vasodilatation, and so on, to compensate for hypoxia . Generally, the human beings could acclimatize to a new altitude in one to three months . This gradual acclimatization may counteract impaired cognitive performance during prolonged exposure to HA . However, the results have been remarkably mixed, with other studies reporting that the cognitive deficit under long-term hypoxia is more severe than the short-term hypoxia (Sharma et al., 2014; G. Zhang et al., 2013). Therefore, more empirical research is needed to provide convincing evidence on how prolonged exposure to high altitude environment affects cognitive processes.

Instead of settling in the plateau, many people return to sea level after short periods of hypoxic exposure at HA. HA deadaptation refers to the process of readaptation to a low-altitude environment involving a series of changes in neural function, metabolism or even structure in acclimatized HA residents. Physiological studies have shown that returning to sea level requires approximately one week for the arterial partial pressure of carbon dioxide (PCO2) to normalize . Biochemical parameters such as Hypersensitive C-reaction protein (hsCRP) and homocysteine returned to baseline level following return to sea level one month compared to baseline . Other evidences suggests deficits in neuropsychological functions may also last when sojourners return to sea level . A study investigated visual spatial and visual non-spatial discrimination abilities, found that the behavioral performances and ERP measurements returned to baseline three months after sojourners returned to the lowlands . Whether cognitive processes will recover accompanied by physiological alterations during HA adaptation and deadaptation has rarely been discussed. Investigating how cognitive processes change in the HA environment and the possibility of long-lasting deficits after returning to sea level could promote the understanding of our brain's protective mechanism for survival and neuroplasticity, and ultimately pave the way for neuroprotection.

Summing up, high altitude hypoxia/reoxygenation changes the neuronal activity and physiological activities. Nevertheless, there are several limitations in existing literatures. Firstly, most studies adopt a cross-sectional design to compare HA residents or sojourners with matched sea-level residents, lacking the comprehensive

depiction regarding alterations of cognitive processing under both HA adaptation and deadaptation conditions. Secondly, there are abundant studies concerning higher-order cognitive processes, while perceptual process is often ignored. Thirdly, there are limited studies using ERP methods, with high temporal resolution to index cognitive processing and provide insight into the dynamic neural mechanisms of cognitive processes, which are particularly suitable to monitor hypoxia adaptation.

To fill this knowledge gap, the present study adopted a S1-S2 paradigm to evaluate the underlying perceptual processes electrophysiological mechanisms of lowlanders who sojourned at an altitude and then returned to the lowlands. Based on previous research , we anticipated that after approximately four weeks of acclimatization to HA, compared with baseline in the lowlands, the heart rate (HR) and diastolic pressure (DBP) would be higher, while the peripheral capillary oxygen saturation (SpO2) would be lower; the N170 amplitude would be significantly increased, and the P1 and N170 latency would be significantly shortened in the HA environment. For the deadaptation process, we speculated that physiological and perceptual organization patterns persist as in the HA environment upon return to sea level after one week, but after one month, we expected them to return to baseline.

Methods

Participants

A total of 23 students who came from an aid education team of Xiamen University (Fujian province, China P.R.) were recruited as paid volunteers. Five participants were removed due to noisy EEG data and drug use, which affected the central nervous system. Thus, the final sample consisted of 18 individuals (5 males, mean ± SD age: 19.15 ± 0.99 years). According to the self-report, all participants had normal or corrected-to-normal vision and were right-handed. None of them had any history of alcohol consumption, neurological or psychiatric diseases, hypertension, heart disease, lung disease or chronic altitude sickness. None of the participants had been to HA areas before, except for two team leaders who went to HA for a short stay one year ago. Oxygen supply equipment was not used throughout the study period. Informed consent was obtained from all the participants prior to the experiment.

Stimulus

Sixty natural neutral facial pictures were quoted from the Chinese Standard Emotional Face Picture System . Half of them were male, and half were female. Adobe Photoshop was used to randomly occlude pictures, with an occlusion ratio of 50% for each picture, which makes the perceptual process more difficult. The picture pixel resolution is 260×300 (width× height). Each stimulus appeared in the center of the 17-inch LCD computer screen (resolution 1024×768 pixels, refresh rate 75 Hz).

Experimental Procedure

The physiological parameters and EEG were recorded at four stages. The first test (Test 1) was performed at Xiamen (63 m) approximately one week before participants ascended to HA. After three days on train, all participants arrived in Lhasa (Altitudes: 3658 m) and stayed for two days. Subsequently, the participants stayed in Damxung County (Altitudes: 4300 m) for three weeks, then returned to Lhasa for three days and performed the second test (Test 2) in Lhasa. The third test (Test 3) was conducted within one week after the subjects returned to Xiamen. The last test (Test 4) was performed one month after participants returned to Xiamen (Figure 1).

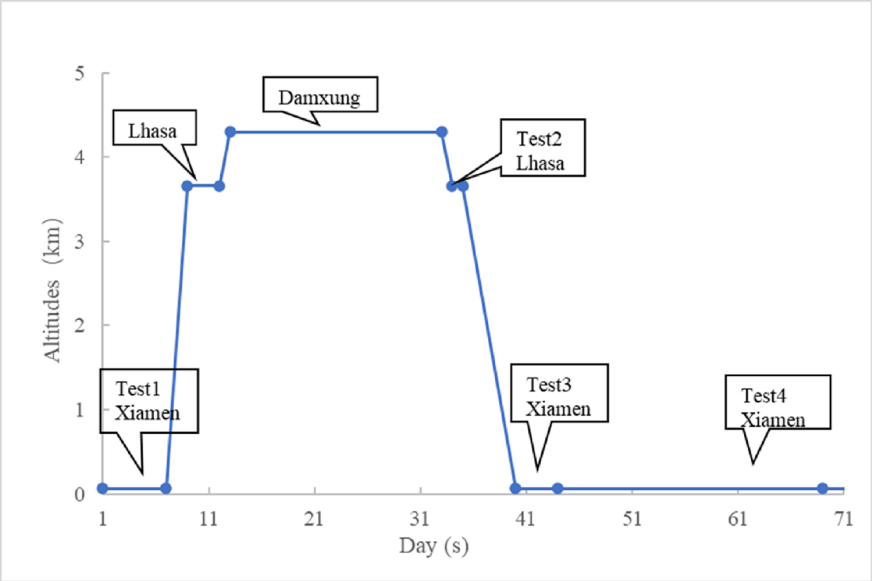

Figure 1. Schematic illustration of the time and altitude of data collection.

Before the EEG recording, HR and SpO2 were measured with a finger clamp pulse oximeter (model DEDAKJ-CMS50D) at rest, vital capacity (VC) was assessed by a digital vital capacity tester (WQS-8888), and an Omron sphygmomanometer (model HEM -7124) was applied to detect resting blood pressure (systolic pressure, SBP and diastolic pressure, DBP).

The EEG experiment lasted approximately fifteen minutes. Participants were seated in a comfortable chair approximately 70 cm in front of the screen in a dimly lit cabin, which subtended 4.8°×6° of visual angle. The facial S1-S2 paradigm was adopted in this study. During the test, 120 trials were randomly presented, and 18 practice trials were used to ensure that all the participants understood the experiment. Two face photographs (S1 is an incomplete face, S2 is an complete face) were presented in order in each trial. All photographs were black and white and keep the same luminance. The probability that S1 and S2 are the same face is 50%. If S1 and S2 are identical, it is the congruent condition; otherwise, it is the incongruent condition (Figure 2). The stimuli were presented by E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). Each stimulus was presented 500 ms on the screen and followed by a blank screen with a "+" in the center. Participants need to figure out whether S1 and S2 are the same face and respond by pressing "F" or "J" on the keyboard. The ISI (interstimulus interval) was 800 ms, and the ITI (intertrial interval) was randomly varied from 800 to 1200 ms.

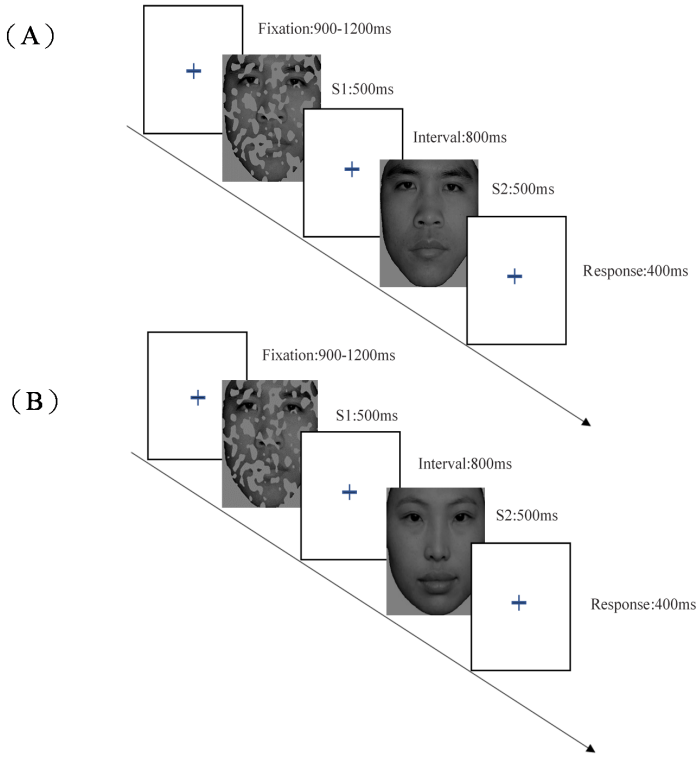

Figure 2 . **Materials and Procedures** (A: Congruent Condition; B: Incongruent Condition)

EEG Recording

EEG data were recorded from a 64 Ag/AgCl electrode cap (Neuroscan Inc.) according to the extended International 10–20 system. The physical reference electrode was placed approximately 2 cm posterior to the CZ electrode. Vertical electrooculographic (VEOG) recordings are electrodes placed above and below the left eye. Two electrodes were used at the outer canthi of both eyes to record the horizontal electrooculogram (HEOG). EEG signals were amplified in DC mode at 100 Hz and digitized at a rate of 500 Hz. The scalp interelectrode impedances of each subject were guaranteed to drop below 5 kΩ.

Data Analysis

One-way repeated-measures analysis of variance (ANOVA) was conducted on physiological data (SpO2, SBP, DBP, HR and VC) separately using time as a within-subject factor.

A 4 (Time: Test 1, Test 2, Test 3, Test 4) × 2 (Face stimulus : incomplete, complete) within-subject design was conducted. Factors are time and condition. The amplitudes and latencies of P1 and N170 are dependent variables. Offline data from the EEG recordings were analyzed using EEGLAB (http://sccn.ucsd.edu/eeglab/), software version 13.5.4b, an open-source signal processing toolbox implemented in MATLAB (The MathWorks, Inc, Natick, USA, Version 2018a). The data were referenced offline to the algebraic mean of all cortical electrodes and filtered offline with a bandpass filter of 1–90 Hz and a notch filter (50 Hz). Trials with various artifacts (body movements, ocular artifacts, or muscle activity) were rejected, with a criterion of +-75 μV from the EEG signal before proceeding to grand averages. Waveform averages for each individual were calculated. Average waveforms were divided into epochs of 1200 ms in length, including a baseline from -200 to 0 ms before the onset of the first face in each trial. Based on previous research, four posterior electrode sites (O1, O2, PO3, PO4) were considered for the analysis of P1. Four electrode codes (P7, P8, PO7, PO8)

from the parietal and parieto-occipital regions were used for the analysis of N170. Peak amplitudes and peak latencies were adopted for statistical analyses for both components.

Three-way, repeated measure analysis of variances was conducted on P1 and N170 amplitudes and latencies separately. Hemisphere (left, right), face stimulus (incomplete, complete) and time (Test 1, Test 2, Test 3, Test 4) are within-subjects factors.

Data were analyzed using SPSS version 22 (Somers, Inc., Chicago) for Windows. All statistical significance levels were two-tailed, with an a priori alpha level for the significance of $p < 0.05$. To explore interaction effects, simple effect analyses were conducted. Effect sizes were calculated through partial eta-squared or Cohen'sd (d). The Greenhouse-Geisser epsilon correction was employed when the data violated the sphericity assumption. A Bonferroni corrected post hoc test was performed to determine pairwise differences.

Results

Physiological Results

The one-way repeated ANOVA revealed a significant main effect of time on SpO2 [F (3, 51) =111.21, $p <$ 0.001, $\eta_p{}^2$ =0.87]. Post hoc comparisons demonstrated that SpO2 in Test 2 was significantly lower than that in the other tests. The main effect of time was significant for HR [F (3, 51) =8.80, $p < 0.001$, $\eta_p{}^2$ =0.34], with higher HR for Test 2 than the other tests. The main effect of time on SBP was significant [F(3, 51) =7.49, $p < 0.001$, $\eta_p{}^2$ =0.31], and SBP was significantly higher in Test 2 than in Test 3. A significant main effect of time was found for DBP [F (3, 51) =26.75,$p < 0.001$, $\eta_p{}^2$=0.61], with larger DBP in Test 2 than in the other tests. There was a main effect of time in VC [F (3, 51) =13.08, $p < 0.001$, $\eta_p{}^2$ =0.44], with a smaller VC in Test 2 than in the other tests (Table 1).

Table 1 . Descriptive statistical results of physiological parameters (M $\pm SD$)

	Test 1	**Test 2**	**Test 3**	**Test 4**
SpO2(%)	98.78±1.17	92.06±2.01	98.56±0.98	98.67±1.24
HR(bpm)	75.83±11.16	88.78±10.30	71.78±11.78	74.00±9.74
SBP(mmHg)	108.00±14.63	113.84±13.63	101.06±11.32	104.28±12.74
DBP(mmHg)	65.44±8.25	76.31±8.25	60.72±5.34	62.67±7.13
VC(ml)	3340.98±976.25	2730.35±760.17	3627.56±1217.78	3671.50±1216.89

ERP Results

P1. For P1 latency, the main effect of time was significant [F (2.11,35.83) = 9.53,$p < 0.001$, $\eta_p{}^2$ = 0.36], with shorter latency for Test 2 than Test 1 (114.04 ± 2.68 ms*vs.* 127.86 ± 2.73 ms,$p = 0.003$), Test 3 (128.85 ± 3.19 ms, $p < 0.001$) and Test 4 (125.72 ± 2.22 ms, $p = 0.001$) (Figure 3). The main effect of face stimulus was significant [F (3,17) = 27.89$p < 0.001$, $\eta_p{}^2$ = 0.62], with longer latency for the complete condition than for the incomplete condition (129.02 ± 1.82 ms *vs.* 119.22 ± 2.43 ms) (Figure 4). No other significant main effects or interactions were found.

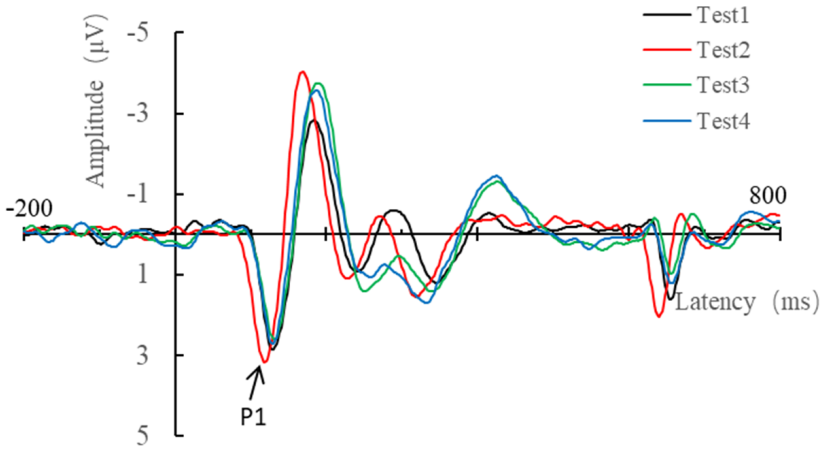

Figure 3. The grand average waveform of P1 from Test 1 to Test 4 (black, red, green, blue line, separately). The two face stimulus (complete/incomplete) and the four electrodes (PO3/PO4/O1/O2) were all averaged.

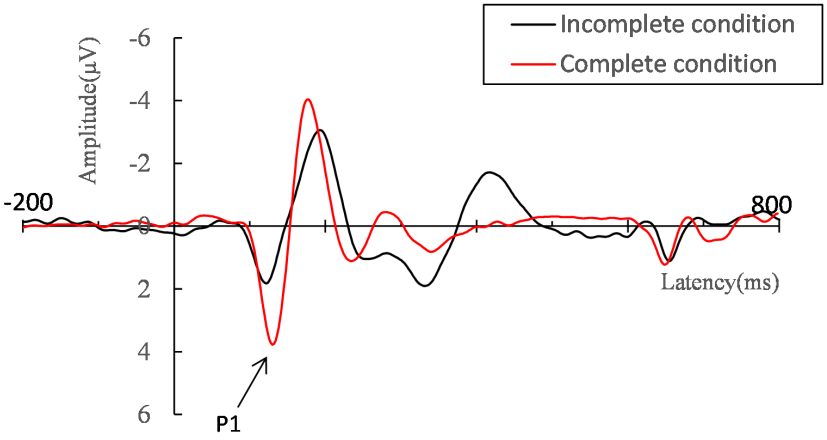

Figure 4. The grand average waveform of P1 elicited in the incomplete face condition and complete face condition . The four tests and four electrode sites (PO3/PO4/O1/O2) were averaged.

For the amplitude of the P1 component, the main effect of time was significant [F (1.72, 29.23) = 3.59, p = 0.02, $\eta_p{}^2$=0.17], and the amplitude of P1 in Test 2 was larger than that in Test 3 (4.70 ± 0.49 *vs.* 3.92 ± 0.46, p = 0.013) and Test 4 (3.91± 0.48, p = 0.010) (Figure 3). The main effect of hemisphere was significant [F (1,17) = 19.64, p ¡0.001, $\eta_p{}^2$ = 0.54], and the P1 amplitude in the right hemisphere was larger than that in the left hemisphere (4.51 ± 0.48 *vs.* 3.81 ± 0.41) (Table 2 and Figure 5). The main effect of face stimulus was significant [F (1,17) = 21.13,p ¡0.001, $\eta_p{}^2$ = 0.55], and the P1 amplitude in the complete condition was larger than that in the incomplete condition (4.72 ± 0.43 *vs.* 3.60 ± 0.48) (Table 2 and Figure 4).

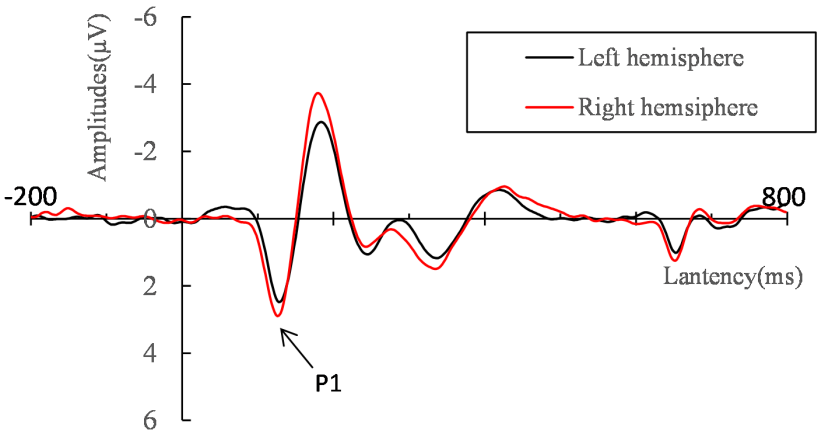

Figure 5. The grand average waveform of P1 elicited in the left hemisphere and right hemisphere . The four tests and four electrode sites (PO3/PO4/O1/O2) were averaged.

Table 2. The peak amplitude and peak latency of the P1 component ($M \pm SD$)

				Face stimulus	Hemisphere	Test 1	Test 2	Test 3	Te
Amplitudes (μ˝)	**Amplitudes (μ˝)**	**Amplitudes (μ˝)**	**Amplitudes (μ˝)**	Incomplete	Left	3.44±1.99	3.44±2.18	2.81±1.88	3.0
					Right	3.87±2.33	4.39±2.67	3.70±2.44	4.1
				Complete	Left	4.46±1.93	5.06±1.93	4.43±2.11	3.8
					Right	4.68±2.02	5.91±2.32	4.74±2.03	4.6
Latencies (ms)	**Latencies (ms)**	**Latencies (ms)**	**Latencies (ms)**	Incomplete	Left	125.94±22.29	109.11±18.68	124.89±21.62	123
					Right	123.50±18.45	104.94±18.69	123.06±22.16	118
				Complete	Left	130.06±11.81	120.50±12.96	136.22±15.84	130
					Right	131.94±7.81	121.61±8.10	131.22±12.27	130

The interaction between time and face stimulus was significant [F (3,51) = 3.84, p = 0.015, $\eta_p{}^2$ = 0.18]. The simple effect test showed that in the incomplete condition, the P1 amplitude was much smaller in Test 3 than in Test 2 (3.25 ± 0.49 μV *vs.* 3.92 ± 0.55 μV, p = 0.042), while under complete conditions, the amplitude in Test 4 (4.24 ± 0.49 μV *vs.* 5.49 ± 0.48 μV, p = 0.003) was smaller than that in Test 2 (Figure 6 and Table 2). No other significant main effects or interactions were found.

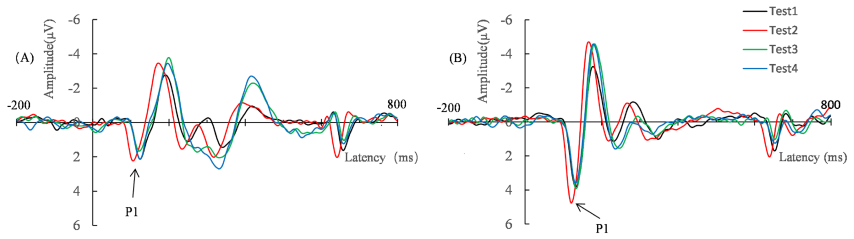

Figure 6. The grand average waveform of P1 elicited in the incomplete face condition and complete face condition from Test 1 to 4 . Four electrode sites (PO3/PO4/O1/O2) were averaged.

N170. The main effect of time was significant for N170 latency [F (2.01,34.08) = 32.87, $p < 0.001$, η_p^2 =0.66], with shorter latency for Test 2 than Test 1 (173.68 ± 2.56 ms *vs.* 188.08 ± 2.29 ms,$p < 0.001$), Test 3 (192.64 ± 2.44 ms, $p< 0.001$) and Test 4 (191.40 ± 2.59 ms, $p < 0.001$) (Figure 7). The main effect of face stimulus was significant for N170 latency [F (1,17)= 57.05, $p < 0.001$, η_p^2=0.77], with longer latency for the incomplete condition (195.57 ± 2.90 ms *vs.* 177.33 ± 1.81 ms) than for the complete condition (Figure 8). The interaction between time and face stimulus was significant [F (3,51) = 6.63,$p = 0.001$, η_p^2 = 0.28]. In the incomplete condition, N170 latency was shorter in Test 2 than in Test 1 (179.25 ± 3.44 ms *vs.* 198.06 ± 3.41 ms, $p = 0.001$), Test 3 (201.89 ± 3.42 ms, $p < 0.001$), and Test 4 (203.08 ± 3.52 ms, $p < 0.001$), respectively. In the complete condition, N170 latency was shorter in Test 2 than in Test 1 (168.11 ± 2.13 ms *vs.* 178.11 ± 2.12 ms, $p = 0.001$), Test 3 (183.39 ± 2.36 ms, $p < 0.001$), and Test 4 (179.72.08 ± 2.10 ms, $p < 0.001$) (Table 3 and Figure 9). No other significant main effects or interactions were found.

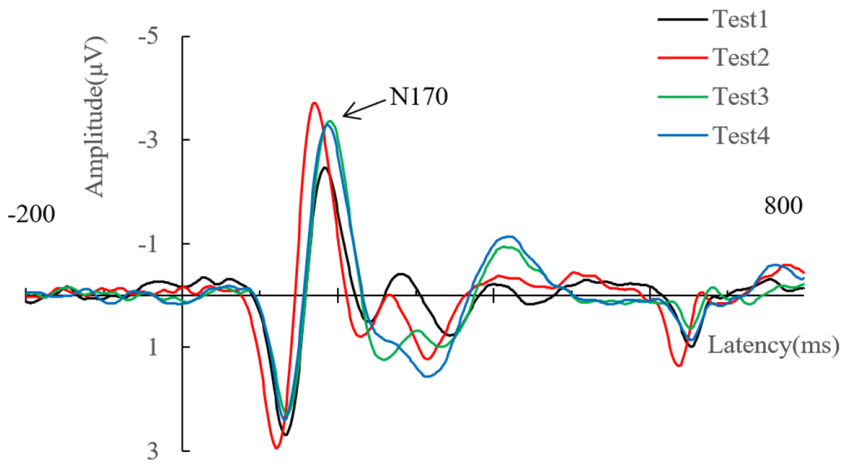

Figure 7. The grand average waveform of N170 from Test 1 to Test 4 (black, red, green, blue, separately). The two face stimulus conditions (complete/incomplete) and the four electrodes (P7/P8/PO7/PO8) were averaged.

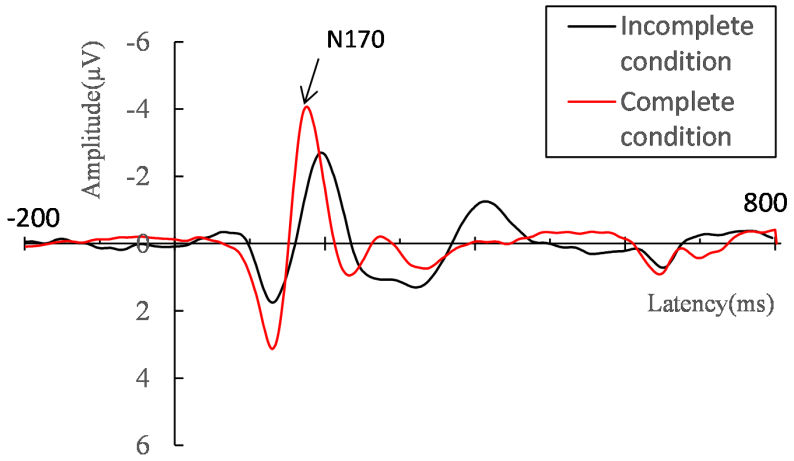

Figure 8. The grand average waveform of N170 elicited in the incomplete face condition and complete face condition . The four tests and four electrode sites (PO7/PO8/P7/P8) were averaged.

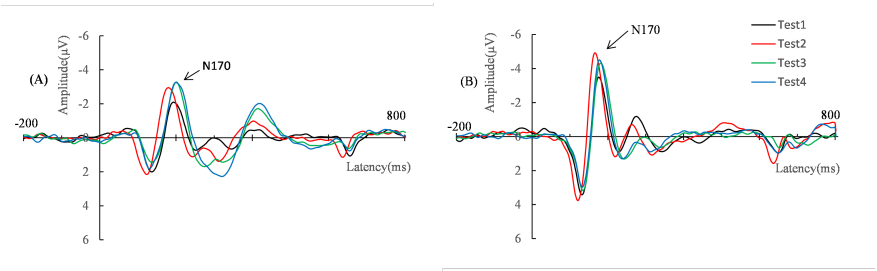

Figure 9. The grand average waveform of N170 elicited in the incomplete face condition and complete face condition from Test 1 to 4. Four electrode sites (PO7/PO8/P7/P8) were averaged.

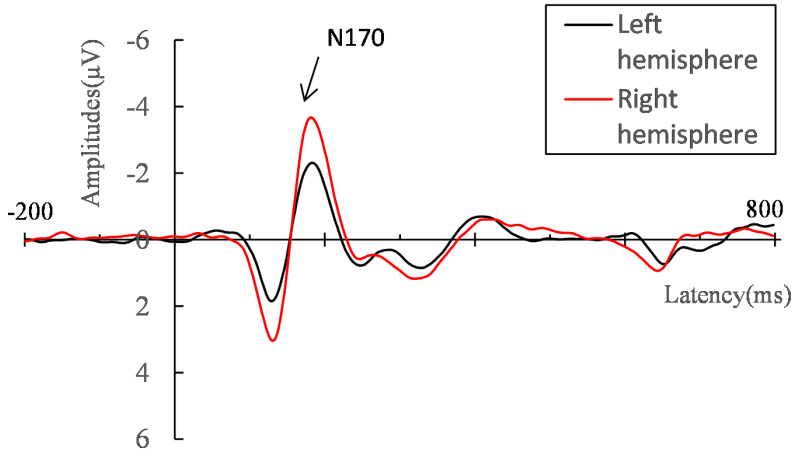

Figure 10. The grand average waveform of N170 elicited in the left and right hemisphere. The two face stimulus (Complete/ Incomplete) and four electrode sites (PO7/PO8/P7/P8) were averaged.

With regard to the amplitude of the N170 component, the main effect of time was significant [F (3,51) = 5.09, p = 0.004, η_p^2 = 0.23], and the amplitude of N170 in Test 2 was larger than that in Test 1 (-5.48 ± 0.59 μV*vs.* -4.17 ± 0.45 μV) (Figure 7). The main effect of hemisphere was significant [F (1,17) = 10.92, p = 0.004, η_p^2 = 0.39], and the amplitude of N170 in the right hemisphere was larger than that in the left hemisphere (-5.48 ± 0.54 μV *vs.* -4.17 ± 0.55 μV) (Figure 10). The main effect of the face stimulus was significant [F (1,17) = 14.27, p = 0.002, η_p^2 = 0.46], and the amplitude of N170 in the complete condition was larger than that in the incomplete condition (-5.50 ± 0.50 μV *vs.* -4.15 ± 0.57 μV) (Figure 8).

The interaction between time and face stimulus was significant [F (3,51) = 7.71, $p < 0.001$, η_p^2 = 0. 31]. In the complete condition, the N170 amplitude was larger in Test 2 than in Test 1 (-6.39 ± 0.60 μV *vs.* -4.55 ± 0.47 μV, p = 0.001) (Figure 9 and Table 3). The interaction between hemisphere and time was significant [F (3,51) = 3.40, p = 0.024, η_p^2 = 0.17]; in the right hemisphere, the N170 amplitude was larger in Test 2 (-5.92 ± 0.60 μV,p = 0.023) and Test 3 (-6.05 ± 0.74 μV, p = 0.014) than in Test 1 (-4.40 ± 0.45 μV) (Fig 11 and Table 3). No other significant main effects or interactions were found.

Table 3. The peak amplitude and peak latency of N170 (M ±SD)

				Face stimulus	**Hemisphere**	**Test 1**	**Test 2**	**Test 3**	**Te**
Amplitude (μ˝)	**Amplitude (μ˝)**	**Amplitude (μ˝)**	**Amplitude (μ˝)**	Incomplete	Left	-3.37±2.55	-3.66±3.35	-3.92±3.01	-4.
					Right	-3.50±2.08	-4.56±3.11	-5.48±3.42	-4.7
				Complete	Left	-3.81±1.94	-5.49±2.66	-4.43±2.33	-4.6
					Right	-5.29±2.29	-7.29±2.84	-6.61±3.24	-6.3
Latency (ms)	**Latency (ms)**	**Latency (ms)**	**Latency (ms)**	Incomplete	Left	199.83±19.91	178.29±19.21	203.94±18.17	20
					Right	196.28±12.14	180.22±15.18	199.83±17.65	20
				Complete	Left	178.17±11.30	167.83±10.79	183.67±12.87	18
					Right	178.06±8.05	168.39±8.90	183.11±8.30	17

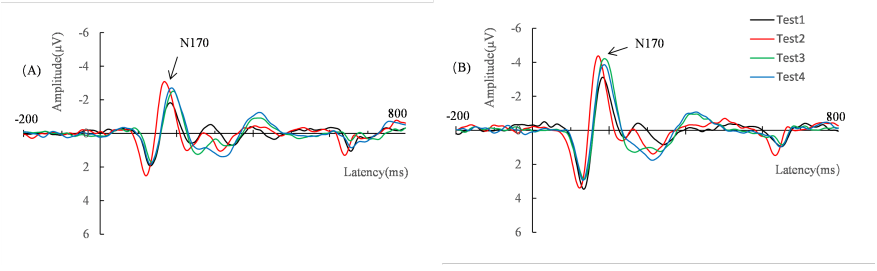

Figure 11. The grand average waveform of N170 elicited in the left and right hemisphere from Tests 1 to 4 (**A** : Left;**B** : Right)**.** The two face stimulus (Complete/ Incomplete) were averaged.

Discussion

The present study used a follow-up method to investigate the change in perceptual organization during HA adaptation and deadaptation. For the adaptation process, compared with the sea level baseline, increased HR and DBP and decreased SpO2 and VC were found when entering HA. Shorter latencies of P1 and N170 showed a faster process of perceptual organization, as well as a larger amplitude of complete face N170. For the deadaptation process, all physiological parameters recovered to baseline levels one week after returning to sea level. Compared with HA, the amplitude of the P1 component of the incomplete face decreased after one week, while that of the complete face decreased after one month. The right hemisphere N170 amplitude increased after entering HA and one week after returning to sea level but returned to baseline one month later. The changes in physiological data and ERP components were out of sync; the perceptual organization function recovery takes a relatively long time. These findings offer novel insights into the neural mechanism of HA adaptation and deadaptation on cognitive processes, especially in the nonprefrontal domain.

After twenty-five days of HA exposure, shorter P1 and N170 latencies were observed, consistent with previous chronic (two-year) HA exposure study . The results suggested that higher levels of cortical excitation within the visual cortex leads to a faster perceptual process when entering HA. After staying at HA for approximately four weeks, the organism is in a state of hypoxia stress. The reduced SpO2 and VC and increased HR and DBP revealed a decrease in the partial pressure of oxygen under a hypoxic environment at HA, causing sympathetic nerve excitement, which may lead to faster perceptual processing. This acceleration is compatible with previous studies that reported that the resting EEG of people who first arrived at HA had enhanced β wave activity, which is a manifestation of increased excitability and excessive alertness in the cerebral cortex . According to a previous study, hypoxia results in the facilitation of perception tasks . The perception task involves activating sensory cortices, which are greatly influenced by neurotransmitter activity, including dopamine (DA), 5-hydroxytryptamine (5-HT), and peptide corticotropin releasing factor (CRF). HA exposure induces high concentrations of neurotransmitters, leading to massive anoxic depolarization of neurons in cortical tissues and causing brain hyperexcitability , which could positively affect perceptual process speed. Existing studies have also suggested that cognitive performance decreased obviously when SpO2 was 80%, but activation and increased performance were observed when SpO2 was 90%, and this activation could have a general stimulating effect on central nervous system (CNS) functional adaptation to the impacts of hypoxia , which may reflect a mechanism attempting to restore/protect neuronal homeostasis . Therefore, it might be interpreted as an adaptive trait rather than a deficit, perhaps attenuating hypoxemia effects under mild hypoxia. Further studies are needed to provide definitive conclusions on the mechanisms relating to the acceleration of perceptual organization processing under HA adaptation.

The N170 amplitude was larger than that at sea level after entering HA for twenty-five days, which was also similar to the result of two years of exposure . The increased N170 amplitude under HA adaptation may be related to maintaining the facial configural encoding process efficiency during hypoxic stress, as certain cortical areas were activated to a greater extent to compensate for decreased processing efficiency due to HA exposure . The increased N170 amplitude may indicate a higher level of neural activity at HA . Interestingly, similar observations in terms of the N170 enhancement phenomenon were also found among elderly adults, which may be due to an increase in the sensitivity to visual stimuli or a decline in brain adaptability with aging . A recent study revealed that cognitive resources were insufficient under HA exposure during a visual attention paradigm, which is similar to normal aging . Moreover, hypoxia was found to accompany inflammatory brain states, such as neurodegeneration . Evidence underscores that hypoxia triggers both the accumulation of cerebral amyloidogenesis and tau phosphorylation, the pathological markers of Alzheimer's disease, which are featured cognitive aging . Chronic exposure to an HA environment may have a similar neural mechanism to cognitive aging, or chronic exposure to HA may accelerate brain aging, but this inference needs more evidence to be confirmed.

After returning to sea level, the body makes adjustments to adapt to the sea level, and all the physiological parameters (SpO2, VC, HR, SBP and DBP) recover to baseline. Compared with HA, SBP decreased one week after returning to sea level, even though it had not been significantly altered by HA adaptation. These

findings imply that the autonomic nervous system outcomes induced by HA exposure are reversible within one week after returning to low altitudes. P1 and N170 latency also returned to baseline less than one week after descending to lowlands, suggesting that the change in the perceptual process was also reversible after returning to sea level. However, hypoxia was found to have a longer lasting effect on brain activity than on blood, which might be because the brain consumes the most oxygen and is more sensitive to hypoxia . Cortical activation recovery under the HA deadaptation process always took more than one week in previous studies . A neuroimaging study showed that entering the HA or returning to sea level in one week were both associated with a sustained greater level of excitement in the posterior parietal cortex and occipital cortex, which are the foundation of the perceptual processes . A longitudinal EEG study also conforms to this view; increased beta power was found after one month of HA exposure (3,800 m), and reoxygenation occurred seven days after returning to sea level, which revealed a sustained higher level of cortical excitation within the visual cortex during HA deadaptation, which may be explained by the rise in capillaries induced by chronic hypoxia . The latency recovered to baseline sooner in our study, which indicates that the change in cortical activation may not be the direct cause of the change in latency. The change in latency may be modulated by a more basic physiological process, which may also regulate the activation of the cortex. The subtle changes in perceptual organization observed here may be a result of synergistic interactions between physiological deadaptation and the aftereffect of hypoxia on neurons . The physiological mechanism of latency changes and its relationship with cortical activation need to be further studied.

During the deadaptation process, compared with HA, the incomplete P1 amplitude decreased one week after returning to sea level, while the complete P1 amplitude decreased after one month. As the P1 amplitude was associated with attention arousal , the decrease in the P1 amplitude may reflect lower arousal to the low-level visual features during the HA deadaptation process. An MRI study was conducted on participants who carried out the same task following the same schedule and found that after one week of reoxygenation exposure, cell activity was inhibited in the visual cortex . This implied that the low-level face perception process was inhibited for sojourners who went through the deadaptation process because of the shortage of sufficient arousal. Although this initial visual processing of faces under both the incomplete condition and complete condition in the deadaptation process showed no difference compared to the baseline at sea level, the low-level face perception process of incomplete faces and complete faces was different after HA deadaptation. This may be because compared with the complete face, the processing of incomplete faces involves not only parietal lobe activity but also frontal lobe activity to compensate for incomplete visual information . After returning to sea level, this compensation mechanism of incomplete faces soon disappeared, so the P1 amplitude decreased in one week. For complete faces, attention arousal decreased gradually, leading to progressively smaller P1 amplitudes.

Seven days after descending to the lowlands, the N170 amplitude remained larger in the right hemisphere, but it was no longer detectable after one month, indicating that it takes more than one week but less than one month for configural face-encoding processing to recover to baseline. This face processing configuration stage is also reversible, although slower than autonomic nervous system recovery. Previous studies found physiological retention (arterial blood gases and hemoglobin) of adaptation after returning to sea level after seven days. During hypoxia in rats for three weeks, microvessels in the brain significantly increased, and remained elevated after reoxygenation . Therefore, the found N170 retention might be relevant to physiological responses that we had not measure or molecular and cellular responses in the brain . Only a tentative interpretation is possibly based on the present data, and further studies should be conducted to elaborate the neural mechanisms.

Both P1 and N170 tend to exhibit a larger amplitude in the right hemisphere than in the left hemisphere , and this dominance of face perception in the right hemisphere did not change under HA exposure. Our results also revealed that the complete face still evoked larger P1 and N170 amplitudes than the incomplete face in the HA exposure condition. Moreover, P1 latency for incomplete faces is shorter than that for complete faces, while N170 latency is longer in incomplete faces than in complete faces . This pattern represents the basic law of face perception organization processing, which was not altered by HA adaptation or deadaptation.

Notably, there are several limitations regarding the current study. First, it lacks a sea level control cohort. Moreover, we did not collect ERP data when participants arrived at HA immediately because hair washing is not recommended within three days of arrival at HA to prevent cold. Further study could assess the acute effects of HA exposure on perceptual process and compare it with chronic HA exposure condition. One more limitation is that we examined healthy, young, and prepared university students during an incremental ascent. Before entering HA, they had regular exercise training and took nutrition products in advance to prevent any possible sickness. As such, some generalization to a broader population may be limited.

Following the limitations outlined above, it would be advisable to replicate our findings in different altitude exposure circumstances (e.g., different HA durations, different altitudes, and different rates of ascent). Another useful addition to the design would be to elucidate the impact of HA adaptation and HA deadaptation on other cognitive function types. Finally, future studies could broaden existing research by investigating the specific relationships between physiological parameters (such as cerebrovascular and cardiovascular parameters) and cognitive alterations, especially how physiological and biochemical activities regulate neuronal activities.

Conclusion

In summary, using ERP, we demonstrated that the perceptual process changed under both HA adaptation and HA deadaptation. The present study suggests that HA adaptation accompanies increased occipital lobe excitation and more neural resources are recruited during the configural encoding stage. Moreover, this change in perceptual organization is reversible after returning to sea level, although low-level feature processing for complete and incomplete faces is different after deadaptation due to the compensation mechanism of incomplete faces, which leads to quicker recovery. Simultaneously, the recovery of the configural encoding stage requires more than one week but less than one month. The present longitudinal study provides a persuading picture clarifying how HA hypoxia/reoxygenation affect perceptual processes, and enables us to shed light on how the human brain acclimates to hypoxia environments.

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Reference