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Cognitive functions and cerebral oxygenation changes during acute and prolonged hypoxic exposure

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HIGHLIGHTS

- Concomitant cognitive performance and hemodynamic response were investigated during high-altitude exposure
- Hypoxia impacted processes involved in cognitive control as well as in temporal judgments
- Prefrontal cortex activity measured with NIRS may counteract the deleterious effects of hypoxia

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ABSTRACT

The present study aimed to assess specific cognitive processes (cognitive control and time perception) and hemodynamic correlates using functional near-infrared spectroscopy (fNIRS) during acute and prolonged high-altitude exposure. Eleven male subjects were transported via helicopter and dropped at 14 272 ft (4 350 meters) of altitude where they stayed for 4 days. Cognitive tasks, involving a conflict task and temporal bisection task, were performed at sea level the week before ascending to high altitude, the day of arrival (D0), the second (D2) and fourth (D4) day at high altitude. Cortical hemodynamic changes in the prefrontal cortex (PFC) area were monitored with fNIRS at rest and during the conflict task. Results showed that high altitude impacts information processing in terms of speed and accuracy. In the early hours of exposure (D0), participants displayed slower reaction times (RT) and decision errors were twice as high. While error rate for simple spontaneous responses remained twice that at sea level, the slow-down of RT was not detectable after 2 days at high-altitude. The larger fNIRS responses from D0 to D2 suggest that higher prefrontal activity partially counteracted cognitive performance decrements. Cognitive control, assessed through the build-up of a top-down response suppression mechanism, the early automatic response activation and the post-error adjustment were not impacted by hypoxia. However, during prolonged hypoxic exposure the temporal judgments were underestimated suggesting a slowdown of the internal clock. A decrease in cortical arousal level induced by hypoxia could consistently explain both the slowdown of the internal clock and the persistence of a higher number of errors after several days of exposure.

1. Introduction

With the emergence of high altitude leisure and sport such as mountaineering, hiking and skiing, an interest on the effects of hypoxia on physiological and cognitive functions has increased substantially. The total atmospheric pressure exponentially decreases with altitude and consequently the partial pressure of oxygen is reduced in arterial blood and in tissues [1]. At altitudes below 15 000 ft (4 572 m), adaptive

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physiological responses usually allow humans to cope with the hypoxic environment. However, even if humans seem hypoxia-tolerant, some authors wondered whether the biological costs of hypoxic adaptations can sometimes out-weigh their benefits [2]. The onset and the severity of symptoms associated with hypoxia are multifactorial and depend on altitude levels, rate of ascent, exposure duration, physical activity and individual response variability [3].

Sensory effects, such as the visual perceptual decrements induced by hypoxia are well documented [4,5], but the effect of hypoxia on higher-cognitive processes remains unclear. Some studies have suggested an impairment of cognitive functions (e.g., [6]), whereas some others failed to observe changes (e.g., [7,8]). These discrepancies are mainly explained by differences in the methods used. The cognitive tasks used are heterogeneous and performances were measured either during high altitude expedition or at simulated altitude, with various durations and severities of hypoxia, and with or without preliminary acclimatization. The variations in these parameters are likely to increase intra subject variability and subsequently, lead to equivocal results (for review see [9]). Using a full test battery of cognitive tests, some recent studies have investigated acute alterations of cognitive performance in hypoxia [7,10,11,12]. This type of testing is relevant for a global evaluation of the impact of hypoxia on cognitive processes, however it does not provide specific cognitive processes evaluation. In the present study, two cognitive processes continuously involved in any goal-oriented behaviors have been specifically targeted. More specifically, changes in cognitive control and time estimation have been investigated using well-established cognitive tasks (respectively, a conflict task and a temporal bisection task) in eleven subjects dropped at 14 272 ft (4 350 meters) of altitude where they stayed for several days. The purpose was to determine whether the ability to inhibit prepotent responses and to estimate time appropriately are impaired by acute and prolonged high-altitude exposure.

Although mean reaction time (RT) and average error rate do provide valuable information relative to cognitive processes, the dynamic analysis of responses provides much more precise information on specific cognitive processes compared to global measures, such as mean RT and error rates classically used in most studies. Indeed, by plotting accuracy rates against RT (known as conditional accuracy functions, CAF) and the magnitude of interference effects as a function of response speed (so-called delta plots) [13,14,15], we should then be able to determine whether the vulnerability to impulsive response activation or the ability to inhibit prepotent responses or both are impacted by high-altitude exposure.

Considering recent findings which show an efficient response inhibition upon exposure to extreme conditions [16, 17, 18], we assume that response inhibition (which is an important aspect of cognitive control) is probably not altered by hypoxia. Data from experiments on time perception have often shown that the subjective duration of a stimulus can be influenced by various factors. The two most documented effects are that subjective duration depends on attention allocated to time (for review, see [19]) and on arousal level [20,21,22]. Investigating time estimation under high altitude exposure could then help to determine whether arousal and/or attention levels are disrupted by hypoxia, two processes which usually remain combined in most studies. Reduced oxygenation in the prefrontal cortex (PFC) has been observed during sustained hypoxia [1], however to the best of our knowledge no studies have been published regarding changes in PFC oxygenation concomitant to changes in cognitive performance during high-altitude exposure. According to the compensation-related utilization of neural circuits hypothesis [23], specific cortical areas may be activated to a larger extent in order to compensate for reduced processing efficiency due to high-altitude exposure. Hence, we hypothesized that i) cognitive control and time estimation would be impaired during acute high altitude exposure and partially restored after partial acclimatisation, while ii) PFC oxygenation would be reduced at high altitude but would be activated during cognitive task to a larger extent compared to sea level, possibly to compensate for reduced oxygen availability at altitude.

2. Methods

2.1. Subjects

Eleven male subjects (mean ± SD, age 28 ± 8 years, height 176 ± 7 cm, weight 71 ± 7 kg) participated in this study after giving written, informed consent. All participants underwent full medical screening before inclusion to rule out respiratory, cardiovascular, and cerebrovascular diseases. Subjects were regular recreational climbers with no history of severe acute mountain sickness (AMS) during previous high-altitude ascents and were not acclimatized to high altitude (no sojourn above 1 500 m over the past 3 months). They received no treatment to prevent or treat AMS throughout the study. The study was approved by the local ethics committee (CPP Grenoble Sud Est V) and was conducted according to the Declaration of Helsinki (Clinical trial registration: NCT01565603).

2.2. Experimental design

The subjects were required to come to the laboratory in Grenoble (212 m) twice prior to the ascension. The first visit served to complete clinical examination and to familiarize the participants with the cognitive tasks in order to stabilize performances and minimize learning effects later in the protocol (i.e., 384 trials for the Simon task, as many trials as necessary to achieve 80% accuracy in the temporal task). The second visit was carried out the week before ascending to high altitude in order to collect baseline data at sea level (SL). The subjects were asked to perform the cognitive tasks and to complete questionnaires (i.e., Lake Louise Score, Environmental Symptom Questionnaire ESQ-III AMS-C). The day of ascension corresponding to D0, subjects underwent helicopter transport to be dropped within 10 min at an altitude of 4 350 meters (Observatoire Vallot, Mont Blanc, Chamonix, France) where they stayed for 4 days. For all the subjects, the cognitive tasks were performed on the day of arrival (D0, between 3 and 5 hours after arrival), the second (D2) and the fourth (D4) day at the same time of the day. The questionnaires were completed every day. Subjects stayed within the facility of the *Observatoire Vallot* from D0 to D4, without climbing or engaging in any other prolonged physical activity. Other physiological investigations were performed during the stay at altitude (echocardiography, etc) with sufficient resting period between measurements to avoid influencing the outcomes of the present study. Subjects were under continuous medical supervision and medical equipment for emergency and acute care was available.

2.3. Questionnaires and arterial oxygen saturation

The symptoms associated with AMS consist of headache, general fatigue, insomnia, dizziness, loss of appetite, nausea and vomiting. Subjects were required to complete self-reported questionnaires for AMS evaluation according to the Lake Louise Score (LLS, 5 items: headache, gastrointestinal problems, insomnia, fatigue and dizziness) [24] and the cerebral sub-score of the Environmental Symptom Questionnaire (ESQ-III AMS-C, 11 items: light-headed, headache, dizziness, feeling faint, dim vision, off-coordination, feeling weak, sick to stomach, loss of appetite, feeling sick and feeling hung-over) [25] on each of the testing days. The presence of AMS was defined as LLS > 3 and ESQ-III AMS-C ≥ 0.6.

Arterial oxygen saturation (SpO_2) was measured using finger-pulse oximetry (Biox 3740 Pulse Oximeter, Ohmeda, Louisville, CO) after 30-s signal stabilization and finger warming with a warm glove for the duration of 2 min (room air temperature: 23 ± 2 °C at sea level and 21 ± 2 °C at altitude).

2.4. Cognitive tasks

2.4.1. Simon task

The participant was sitting on a chair 1 meter away from the computer screen and was provided with hand held response keys to

complete the task. During the whole trial participants had to fixate on a white point, positioned in the centre of the screen and they were required to respond, as quickly and accurately as possible, by pressing the appropriate response key according to the shape (i.e., square or circle) of a geometric symbol delivered either to the left or to the right of the fixation point. The distance from the centre of the white fixation point to the centre of the geometric symbol located to either the right or left was 7.5 cm. Participants had to respond according to the shape of the symbol while ignoring its spatial location. The mapping of geometric symbol shape to response key (for example, right response for a square and left response for a circle) was counterbalanced across participants. The task included two equiprobable trial types: the congruent trials (CO) (response side ipsilateral to stimulus side), and the incongruent trials (IN) (response side contralateral to the stimulus side). As soon as a response key was pressed or when a delay of 1.5 s after the stimulus onset had elapsed without a response, the stimulus was removed from the screen and the next trial began.

The familiarization phase of the Simon task consisted of 4 blocks of 96 trials (each block lasted approximately 3 min 45 s with an approximate 3 min 'cognitive rest' interval between each block), and the same procedure was followed in the test phase performed at SL and at altitude.

For chronometric analysis, the cumulative density functions (CDF) of correct trials were estimated for each participant and averaged through the so-called "vincentizing" procedure [26]: single-trial RT were rank ordered for each type of trial separately (CO trials and IN trials), and binned into deciles of equal frequencies (same number of trials). The mean of each bin was computed and equivalent bins were averaged across participants. Delta-plots were constructed by plotting the difference between incongruent and congruent bins, as a function of the mean incongruent and congruent bin values (for more information, see [27,28]). For distributional accuracy analysis, correct and erroneous trials were mixed together and the resulting distributions were vincentized as described above. For each bin, the proportion of correct trials was computed along with the mean RT of the bin. These couples of data were averaged per bin through participants. This provides the CAF representing the mean accuracy as a function of increasing RT.

2.4.2. Time perception task

The time perception ability of participants was evaluated through two auditory temporal bisection tasks, one involving a short duration range (centred on 250 ms) and the other one a long duration range (centred on 2000 ms). The task was to judge the duration of a white noise.

For each duration range, participants undertook a training phase before the test phase. In the training phase, only the anchor durations were used (190 ms and 310 ms for the short duration range and 1520 ms and 2480 ms for the long duration range). The training phase consisted of two parts. First, participants were presented with the two standard anchor durations, each presented four times in alternation. Participants were instructed just to listen to the auditory stimuli, with no response required. The experimenter indicated to the participants whether a stimulus was "short" or "long" in concurrence with its presentation. Next, the two anchor durations were randomly presented ten times, and subjects indicated whether the auditory stimulus presented was short or long by pressing the appropriate response key, using either the right or the left index finger. The association between the response (short or long) and the hand used (right or left) was counterbalanced between participants. Feedback was not given after each response but at the end of the block of 10 trials only. The training phase was validated if the participants obtained a performance level equal or above 80%. If not, the training session was performed again. In the test phase, white noise could be of five different durations (for the short duration range: 190 ms, 220 ms, 250 ms, 280 ms, 310 ms and for the long duration range: 1520 ms, 1760 ms, 2000 ms, 2240 ms, 2480 ms). Participants were required to indicate whether the presented stimuli were short or long by pressing the appropriate response key. Feedback was not given. Each session contained two blocks of 50 trials corresponding to a stimulus of five different durations, each delivered ten times (inter-trial interval was 2 s).

The classification data obtained in the temporal bisection procedure may be quantified as the proportion of long responses the participant made at each signal duration and can be well described by a sigmoid function. Sigmoidal functions were fitted to the response functions of each participant to estimate the two dependent variables: the point of subjective equality (PSE) and the difference limen (DL). The PSE is the signal duration at which a participant is equally likely to classify the signal as short or long. It represents the subjective midpoint between the short and long anchor values that the participant learned during the training phase. An increase in the PSE (a rightward shift of the psychometric function) means that participants chose more often to respond "short", inversely a decrease in the PSE (a leftward shift of the psychometric function) means that participants were biased towards responding "long". The PSE, reflecting a shift of the psychometric function, therefore allows us to observe whether the participants presented a bias in their temporal judgements towards either an underestimation or an overestimation of durations. The DL is a measure of the "slope" of the participants' response function when plotted. It is calculated by subtracting the duration that the participant classifies as long 25% of the time from the duration that the participant classifies as long 75% of the time and dividing by two. It can be interpreted as a measure of participants' temporal precision because steep slopes are indicative of precise temporal processing whereas shallow slopes indicate greater variability in the interval-timing system. Both indices were calculated using a linear regression method.

2.5. Near-Infrared Spectroscopy data collection and processing

Brain activity leads to an increase in oxygen consumption, which is accompanied by an increase in cerebral blood flow due to neurovascular coupling. This change in the local oxygenated (HbO_2) and deoxygenated (HHb) haemoglobin can be assessed using NIRS technique during cognitive tasks [29,30]. Based on NIRS signals, neural activation is typically expressed as an increase in [HbO_2] accompanied with a slight decrease in [HHb] [31]. In the present study, changes in [HbO_2] and [HHb] levels were collected during the Simon conflict task by a continuous wave NIRS device (NIRO-300, Hamamatsu Photonics, Hamamatsu City, Japan). NIRS uses light in the near-infrared spectrum to investigate specific properties of biological tissues. The NIRS instrument measures the amount of infrared light that goes from an emitter to a receptor by passing through the investigated tissue. From the received signal, quantitative changes from a baseline in chromophore concentration may be evaluated. In the present study, we used one recording channel consisting of one light-emitter probe (fiber optics irradiating laser beams) and one light-detector probe (photodiode) located 4 cm away from each other on the scalp of subjects over the left prefrontal cortical area at the midpoint between Fp1-F3 (landmarks of the international EEG 10-20 electrode placement [32]). Since the position of the NIRS channel and the absence of contamination through ambient light are of great importance, the optodes were positioned in a black holder stuck on the skin with double-sided adhesive tape. The NIRO 300 employs the method of spatially resolved spectroscopy by means of three small sensors, closely spaced on the detection probe, to measure light attenuation as a function of source–detector distance. From these measurements, a tissue oxygenation index (TOI in %) is calculated from the slope of light attenuation along the distance from the emitting probe. TOI has high sensitivity and specificity to intracerebral changes because it minimises the contribution of superficial layers to the benefit of deep tissue layers [33,34]. To reduce any artefact, subjects were asked to minimize head and body movements. During the 3 min rest period between blocks, subjects were instructed to stay relaxed and keep their eyes open.

In the present study, we used an amplitude-based approach to assess and discriminate the cortical activation changes during the conflict task compared to a reference-resting baseline recorded just before the task [29]. The NIRS raw data were low-pass filtered using a cut-off frequency of 0.7 Hz to remove the heart signal. Then, we calculated the relative hemodynamic changes (Δ) for [HbO_2], [HHb], [Hbtot] = [HbO_2] + [HHb] (in μM.cm) and TOI (%) by subtracting the level obtained during the resting state period (mean value of the last 30 s of each 3-min baseline) and the last part of each artifact free stimulation period (mean value over 30 s during the last minute of each conflict task block). For each experimental condition (SL, D0, D2 and D4), the NIRS data were block-averaged. While one usually focuses on HbO_2 measurement for the determination of cortical activation due to its better signal-to-noise ratio (relative to HHb) following a functional task, extracortical changes due to systemic changes (e.g., blood pressure, heart rate, skin blood flow) are more likely to influence HbO_2 than HHb [35]. Consequently, for rejecting interference from extracortical changes expected to occur during NIRS monitoring due to the altitude stress, we considered ΔTOI and ΔHHb variables as main indicators of the cerebral hemodynamic changes.

Finally, absolute cerebral tissue oxygenation index (i.e., TOI) which is known to be affected by changes in arterial oxygen saturation and end-tidal carbon dioxide tension [36] was calculated during the first baseline period (mean of the 30 s preceding the first block of conflict task) to provide information on the altitude effects.

2.6. Statistical analysis

Repeated measures within subjects ANOVA was performed on each dependent variable (i.e., mean RT, decision error, distributional analysis, post-error adjustments, PSE, DL and the self-report measures, Δ[HbO_2], Δ[HHb], Δ[Hbtot] and ΔTOI, and absolute TOI). Greenhouse-Geisser degrees of freedom correction was applied when the test of sphericity was violated. Newman-Keuls posthoc tests were performed on each significant interaction and on main effects when necessary. Effect sizes were calculated using Partial Eta Squared. Significance was set at $p < .05$ for all analyses. All error bars on the Figures represent standard errors of the mean.

To allow for direct comparisons between short and long range duration, we computed normalized indices both for the PSE and the DL. For the index of variability, we used the Weber fraction (WF) which corresponds to the ratio DL/PSE. The normalization of the PSE was obtained by computing the following index: Norm-PSE = PSE/midpoint value, with the midpoint values respectively corresponding to 250 ms (short duration range) and 2000 ms (long duration range). ANOVAs involving Day (SL, D2, D4) and Duration range (short, long) as within-subject factors were then separately performed on these two indices, WF and Norm-PSE.

Exploratory Pearson correlations were also performed between questionnaires (i.e., Lake Louise Score, Environmental Symptom Questionnaire ESQ-III AMS-C), self-rating scales (i.e., intensity of headache and general fatigue) and cognitive performances (mean RT, error rate). Finally, Pearson's correlations were performed between altitude-induced NIRS variables and RT performance changes based on the mean value at D2 and D4 relative to D0.

3. Results

One participant was too affected by AMS to perform the Simon task on D0 and two participants did not comply to the instructions given for the Simon task. The data of these participants could not be taken into account. Consequently the following analyses include 8 participants except for the temporal bisection task and the cerebral oxygenation responses.

Unfortunately, due to technical problems (not linked to the temporal bisection task) and an already very busy testing schedule, 6 participants were not able to carry out the temporal bisection task during the first day at high altitude (D0). This lack of data did not allow for the inclusion of the D0 results in the temporal bisection task analyses. Consequently the analyses of the temporal bisection task include 11 participants for 3 testing days (SL, D2 and D4 at high altitude).

3.1. Simon task

3.1.1. Global performance

3.1.1.1. Reaction Times. The mean RT was submitted to an ANOVA with Day (SL, D0, D2, D4) and Congruency (CO, IN) as within-subject factors. Results showed a main effect of congruency ($F(1,7) = 48.39$, $p < .001$, $\eta 2 = .87$) with slower RT for IN trials (367 ± 9ms) compared to CO trials (343 ± 10ms) and a main effect of Day ($F(3,21) = 6.21$, $p = .003$, $\eta 2 = .47$). Participants displayed slower RT in the early hours of exposure at high altitude (D0: 373 ± 11ms) compared to the mean RT observed at SL (346 ± 8ms; $p < .01$). The RT lengthening was no longer detectable after 2 days (D2: 346 ± 9ms; $p = .96$) and 4 days (D4: 354 ± 13ms; $p = .26$) at high altitude (Fig. 1A). The Day × Congruency interaction was not significant ($F(3,21) = 2.64$, $p = .10$, $\eta 2 = .27$) showing that the interference effect was similar at SL and at high altitude at any time.

3.1.1.2. Decision Error. The arcsine transformations of the error rate were submitted to an ANOVA with Day (SL, D0, D2, D4) and Congruency (CO, IN) as within-subject factors. Analysis showed a classic significant effect of Congruency ($F(1,7) = 17.57$, $p = .004$, $\eta 2 = .72$), illustrating the prevalence of more errors for IN trials (8.85 ± 2.1%) than for CO trials (5.64 ± 1.2%), and a significant Day × Congruency interaction ($F(3,21) = 3.47$, $p = .03$, $\eta 2 = .33$). In the early hours of exposure, the decision error for CO trials increased and became almost twice as high compared to that observed at sea level (SL: 3.5 ± 0.9% vs D0: 5.91 ± 0.9%, $p < .01$) and remained high during the 4 days at high-altitude (D2: 5.92 ± 0.9%, $p < .05$; D4: 7.23 ± 1%, $p < .01$) (Fig. 1B). Interestingly, the propensity to commit decision errors for IN trials was not different at SL (8.5 ± 1.3%) and at high altitude (D0: 9.2 ± 1.7%; D2: 9.2 ± 1.1%; D4: 8.5 ± 1.5%).

3.1.2. Distributional Analysis

Separate ANOVAs involving Day (SL, D0, D2, D4), Congruency (CO vs. IN) and Deciles as within-subject factors were performed on RT distributions and CAF to determine whether curves diverge with acute or prolonged hypoxic exposure. In line with the activation–suppression model [27], the analysis performed on RT distributions revealed a marginally significant Congruency × Decile interaction ($F(9, 63) = 3.93$, $p = .06$, $\eta 2 = .36$) which suggests that the magnitude of the interference effect decreased as RT lengthened (Fig. 1C). Interestingly, the second order interaction (Day × Congruency × Decile) was not significant ($F(27, 189) = 0.30$, $p = .76$, $\eta 2 = .04$) revealing that high altitude exposure did not change the drop-off pattern observed as RT lengthens. This finding suggests that hypoxia did not alter the build-up of a top-down response suppression mechanism.

Regarding CAF (Fig. 1D), as classically observed, a significant Congruency × Decile interaction was obtained ($F(9, 81) = 38.45$, $p < .001$, $\eta 2 = .67$). More precisely, in the initial phase (first deciles), the error rate was higher for IN trials than for CO trials (1^{rst} decile accuracy: 67 ± 3.7% vs 96 ± 1.3%, $p < .001$; 2^{nd} decile accuracy: 85 ± 1.6% vs 97 ± 1%, $p < .001$). Interestingly, the absence of a second order interaction ($F(27, 189) = 0.81$, $p = .58$, $\eta 2 = .08$) suggests that the propensity to commit fast errors was not influenced by acute or prolonged hypoxic exposure. Therefore, hypoxia would not alter early automatic response activation.

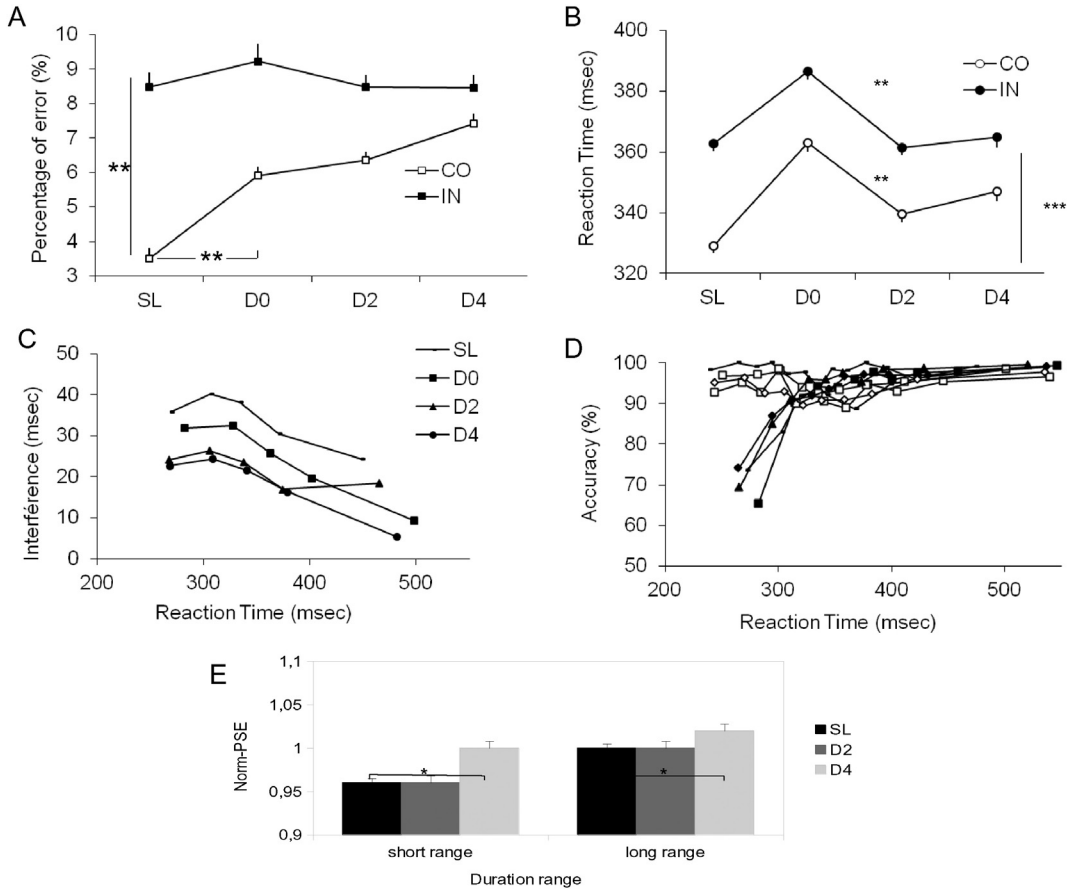

Fig. 1. [A] Mean reaction time (RT) during prolonged hypoxic exposure (n = 8) for congruent trials (CO, empty symbols) and incongruent trials (IN, full symbols). SL = sea level, D0 = first hours of exposure at high altitude, D2 = after 2 days at high altitude, D4 = after 4 days at high altitude. Error bars are mean standard errors; [B] Percentage of decision error (n = 8) during prolonged hypoxic exposure for congruent trials (CO, empty symbols) and incongruent trials (IN, full symbols). SL = sea level, D0 = first hours of exposure at high altitude, D2 = after 2 days at high altitude, D4 = after 4 days at high altitude. Error bars are mean standard errors; [C] Delta plots of RT (n = 8) illustrating the magnitude of the interference (in milliseconds) as a function of reaction time (RT) at sea level (SL) and during hypoxic exposure at D0, D2 and D4; [D] Conditional accuracy function (CAF, n = 8) representing the percentage of accuracy for congruent (CO, empty symbols) and incongruent (IN, full symbols) trials as a function of reaction time (RT) at sea level (SL) and during hypoxic exposure at D0, D2 and D4. [E] Temporal bisection task. Norm-PSE at SL (sea level), D2 (after two days at high altitude) and D4 (after four days at high altitude) for both duration ranges. Error bars are mean standard errors. *** $p < .001$, ** $p < .01$,* $p < .05$

3.1.3. Post-error adjustments

To determine whether hypoxia alters the capacity of proactive control of errors, micro-adjustments between trials were also investigated by examining the trial-by-trial modification of RT [37]. An ANOVA involving Period and Correctness of the preceding trial (correct vs. error) as within-subject factors was conducted to assess post-error adjustments. Results showed a post-error slowing effect ($F(1, 7) = 28.33$, $p = .001$, $\eta 2 = .99$), with RT after an error slower (380 ± 22 ms) than after a correct trial (353 ± 19 ms). The interaction between Day and Correctness was not significant ($F(3, 21) = 1.15$, $p = .34$, $\eta 2 = .14$), suggesting that the between trials adjustments was not affected by acute or prolonged hypoxic exposure.

3.2. Temporal bisection task

Concerning the index of variability, no significant differences were observed on WF, indicating that participants were not more variable in their temporal judgments after hypoxic exposure.

Concerning the PSE which provides information about perceptual bias, analysis of Norm-PSE showed a significant main effect of day ($F(2, 20) = 6.25$, $p = .007$, $\eta 2 = .39$) and of duration ($F(1, 10) = 5.09$, $p = .05$, $\eta 2 = .33$). As revealed by Fig. 1E, the exposure to high altitude leads to bias in temporal estimation. For both durations, the PSE was larger after four days of hypoxic exposure compared to SL ($p = .01$), which indicates that intermediate durations more often judged as long when on SL were more often judged as short after prolonged hypoxic exposure. Participants underestimated durations after four days in altitude. In addition, the absence of significant Day × Duration interaction ($F(2, 20) = 0.63$, $p = .54$, $\eta 2 = .08$) suggests that this effect was of similar size in both durations.

3.3. Questionnaires

The results of the questionnaires were submitted to separate ANOVA with Day (SL, D0, D2, D4) as a within-subject factor. The results of the Lake Louise Score revealed a main effect of Day ($F(3,30) = 9.79$, $p < .001$, $\eta 2 = .49$) showing an increase in AMS symptoms at D0 (4.6 ± 0.8, $p < .001$), and D2 (3.4 ± 0.9, $p = .007$) compared to SL (0.7 ± 0.2). At D4 (1.0 ± 0.4, $p = .75$), the AMS symptoms were not different from baseline. A main effect of Day was reported on the cerebral sub-score of the Environmental Symptom Questionnaire ($F(3,30) = 5.36$, $p = .004$, $\eta 2 = .35$) confirming the presence of AMS at D0 (0.8 ± 0.3, $p = .01$). Exploratory Pearson correlations revealed a significant correlation between ESQ-III AMS-C and RT ($r = .34$, $p = .04$).

3.4. Arterial and cerebral oxygenation changes

SpO_2 decreased from SL (98 ± 0.3%) to high-altitude ($F(3,30) = 140.48$, $p < .001$, $\eta 2 = .93$), where it remained constant from D0 to D4 (D0: 83 ± 1.2%, D2: 82 ± 0.7%, D4: 84 ± 0.7%).

The cerebral tissue oxygen saturation (as expressed by absolute TOI values measured at the beginning of each experimental session during the first rest period) changed significantly according to the day ($F(3,30) = 38.42$, $p < .001$, $\eta 2 = .76$). Post hoc analyses indicated that TOI values declined by 11% ($p < .001$, Fig. 2B) for all days at high-altitude (D0, D2 and D4) compared to SL.

After analysing 170 measurements of NIRS variables during the conflict tasks (11 subjects × 4 days × 4 blocks), the typical NIRS hemodynamic pattern was found (i.e., an increase in [HbO_2] associated with a concurrent decrease in [HHb] was observed in 76% of the measurements). The remaining patterns were a so-called "deactivation" pattern (i.e., inverse NIRS response; about 6%) or no evident changes (i.e., absence of increase/decrease in any haemoglobin species between rest and stimulation periods; about 6%). Note that 13% of the total NIRS measurements were excluded from the analysis due to technical issues. Repeated one-way measure ANOVA revealed a main effect of Day on Δ[HHb] ($F(3,30) = 4.25$, $p < .05$, $\eta 2 = .15$) and ΔTOI ($F(3,30) = 3.06$, $p < .05$, $\eta 2 = .20$) responses, but not on Δ[HbO_2] ($F(3,30) = 1.57$, $p > .1$, $\eta 2 = .08$) and Δ[Hbtot] ($F(3,30) = 1.62$, $p > .1$, $\eta 2 = .01$) responses (Fig. 2A). The post hoc analyses suggested minor differences between SL and D2 conditions (Δ[HHb], $p = .07$, ΔTOI, $p = .09$).

Between D0 and D2, changes in RT showed a significant correlation with changes in ΔTOI ($r = -.75$, $p < .05$) and Δ[HHb] ($r = .74$, $p < .05$) (Table 1), but not with Δ[HbO_2] and Δ[Hbtot]. Between D0 and D4, changes in RT only showed a significant correlation with changes in Δ[HbO_2] ($r = -.81$, $p < .05$). A trend was observed for Δ[Hbtot] ($r = -.64$, $p = .09$).

Table 1
Correlations between cognitive performance and hemodynamic changes during the high altitude stay. Pearson's r and *P* values are reported for each correlational analysis in 8 subjects. Correlations were assessed between the hemodynamic response (changes in oxygenation) and performance (changes in reaction time, ΔRT) variables during the Simon task.

Periods	Performance	Hemodynamic	r	*P*
D0-D2	ΔRT	ΔTOI	- 0.75	**0.03**
		Δ[HHb]	0.74	**0.03**
		Δ[HbO_2]	- 0.37	0.38
		Δ[Hbtot]	0.29	0.50
D0-D4	ΔRT	ΔTOI	- 0.53	0.19
		Δ[HHb]	0.36	0.39
		Δ[HbO_2]	- 0.81	**0.01**
		Δ[Hbtot]	- 0.64	0.09

D0: day of arrival; D2: second day at high altitude; D4: fourth day at high altitude.

4. Discussion

The present study examined cognitive functions and hemodynamic correlates during acute and prolonged high-altitude exposure. Specific cognitive processes, such as cognitive control and time perception, considered as being of great importance in goal-oriented behavior, have been investigated through a conflict task and bisection temporal tasks. Moreover, PFC oxygenation changes have been evaluated during the conflict task by using NIRS.

4.1. Cognitive functions

Three major findings have emerged from this study. Firstly, acute exposure to hypoxia impacts information processing mainly in terms of both speed and accuracy. Secondly, the cognitive control (assessed through an evaluation of response inhibition, impulsivity and post-error adjustment) was unaltered and remained fully efficient after high altitude exposure. Thirdly, increased PFC activity only partially counteracted the deleterious effects of hypoxia on information processing.

In the early hours of exposure, participants displayed slower RT and decision errors were nearly twice as numerous which confirmed the existing literature on hypoxia showing an impairment of cognitive functions (e.g., [6]). The acute exposure to hypoxia at 14 272 ft (4,350 meters) slowed down RT and increased the number of errors only for CO trials, i.e. when subjects had to rapidly produce simple spontaneous responses. This propensity to commit more errors in CO trials was not restricted to the early hours of exposure but persisted during the entire sojourn. On the contrary, impaired RT was no longer detectable after two days spent at high-altitude. It seems that adaptive processes which partially counteract the deleterious effects of hypoxia on information processing occurred in the first days of exposure. Moreover, the RT lengthening observed during acute high altitude exposure could not be explained by difficulties in controlling interference. Indeed, the magnitude of the interference was not altered by high altitude exposure as revealed by the absence of a significant Congruency × Days interaction. These data are confirmed by the dynamic analysis of cognitive control which revealed that hypoxia did not modify the drop-off pattern observed as RT lengthens. The build-up of a top-down response suppression mechanism seems to remain fully efficient.

Two alternative explanations may account for the RT lengthening. High altitude exposure may produce slower motor execution or perhaps this slowing down could result from more general executive deficits, such as alertness or sustained attention impairments. The first hypothesis could be explored in future studies by recording the electromyographic (EMG) activity during a choice RT task (for details see [38]). The decomposition of RT, with respect to the EMG activity of agonist responses, would help to distinguish the effect of hypoxia on sensory processes and on late motor processes. In the case of the latter hypothesis, if the level of alertness or attention was lower in participants due to hypoxia, they could have more difficulty in quickly detecting the

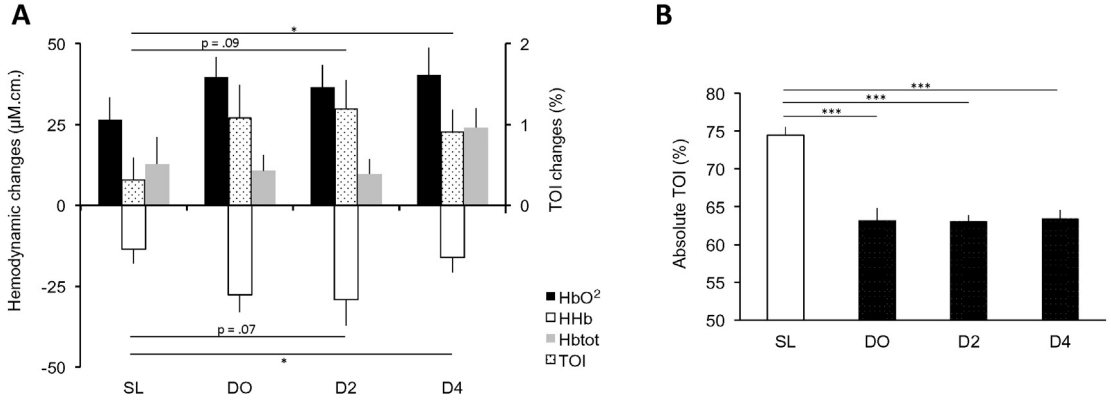

Fig. 2. [A] Bar plots of mean Δ[HbO_2], Δ[HHb], Δ[Hbtot] and ΔTOI, and [B] bar plots of mean absolute TOI (n = 11) at the baseline resting level for the 4 experimental conditions. SL = sea level, D0 = first hours of exposure at high altitude, D2 = after 2 days at high altitude, D4 = after 4 days at high altitude*** $p < .001$, * $p < .05$

stimulus, resulting in all subsequent processing being delayed which would manifest as a longer RT.

This hypothesis may be explored in line with the data obtained in the temporal bisection task. For many years, the prevalent guiding theoretical framework for understanding how we measure the duration of intervals has proposed that we time intervals using an internal clock functioning as a stopwatch, with a clock stage, a memory stage and a comparison stage [39,40]. The clock consists of a pacemaker producing pulses at a given rate and a switch, driven by external stimuli with some latency that controls the access to an accumulator summing the pulses. The present results revealed that exposure to high altitude produced a shift in temporal judgments towards an underestimation of perceived time after several days of reduced oxygenation level. In the framework of the pacemaker-counter model, two hypotheses are possible to explain time underestimation. The first one involves the role of focused attention which determines the quality of pulse accumulation. Under full attention, the switch is supposed to close and to remain closed for the entire duration of the stimulus whereas when less attention is being paid, the switch may oscillate between closed and opened states which would lead to fewer pulses accumulated and then durations judged as shorter. An alternative explanation involved the cortical arousal level which affects the pacemaker rate. If the clock runs less fast, fewer pulses are accumulated and temporal intervals seem shorter, explaining the rightward shift observed in the PSE [22,41]. Since a slowing down of the pacemaker rate is classically associated with a decrease in arousal level, our data would be consistent with the hypothesis that hypoxia would decrease cortical arousal level. Moreover, due to the scalar property characteristic of temporal processing, an effect on the pacemaker rate should be multiplicative with the duration values [41,42]. Indeed, if the pacemaker runs more slowly, the effect has to be greater for longer than for shorter durations (i.e. proportional to the duration values). This seems not to be the case in the present study since no effect of duration was observed on Norm-PSE which means that the size of the effect was similar for both durations. An effect of hypoxia on arousal level seems then possible even if it still remains to be explained why such an effect would be efficient on RT the first day of exposure and then would get reduced and becomes manifest on timing only after four days of exposure. In relation to this, it could be interesting to notice that the adaptation process which occurred between D0 and D2 in the Simon task only partially counteracted the performance decrement induced by hypoxia. Indeed, only the speed of response was restored whereas the accuracy still increased a little more each day. Therefore, we can speculate that the physiological changes induced by a prolonged exposure at high altitude (highlighted by NIRS data, see below) would not allow for a complete restoration of cognitive functions. It is then likely that the participants strategically chose to improve their rapidity to the detriment of their accuracy. The low level of alertness, consistent with data obtained in the temporal task, would then manifest through the increase in error rate still present after four days of exposure.

Lastly, the propensity to impulsivity (investigated by using the CAF) and the capacity of controlling errors (investigated by examining trial-by-trial modifications) were unaltered by acute or prolonged hypoxia. The number of fast errors was not increased and the slowing down after errors was still observed when participants were exposed to hypoxia. These results confirm that online control mechanisms, involved in the correction of incorrect activation, as well as proactive control, remained fully efficient.

To sum up, the results consistently suggest that cognitive control including inhibitory processes, vulnerability to automatic responses, control of interference and proactive control of errors remains fully efficient even in extreme conditions like a drop at 14 272 ft (4,350 meters) of altitude without any medication. This finding does not appear surprising since proficient cognitive control has already been reported during intense physical exercises [43,16], physical exercise maintained until exhaustion [17] or after a complete sleep deprivation [18]. The only process which seems affected and which would explain the global slowing down of participants would be the level of alertness but further studies are needed to more directly tackle this question.

Note that the repeated measure design used in the present experiment does not allow for completely neutralizing practice effects despite a familiarization performed prior to the ascension. It is therefore possible that any cognitive processes impairment observed here may have been underestimated.

4.2. Cerebral oxygenation

In response to exposure to high-altitude hypoxia, cerebral tissue oxygen saturation (absolute TOI) decreased during early exposure (D0) relative to SL and remained low during all days at high-altitude as SpO_2 did. This result, in accordance with previous studies (see for review [44]), supports the idea that cerebral tissue oxygen saturation changed in the early hours of exposure at high altitude (D0), but then remains stable even if the exposure is prolonged during several days (D4). In the present study, a typical hemodynamic pattern corresponding to an increase in HbO_2 coupled with a decrease in HHb as blood flow increases in the active tissue [31], has been observed when the Simon task was performed. This means that the increase in oxygen use is slightly lower than the increase in oxygen delivery, resulting in a relative decrease in oxygen extraction fraction because the supply transiently exceeds the demand. Though fNIRS studies have revealed leftward lateralization for the Stroop effect and correlation with behavioral performance (e.g., [45]), to the best of our knowledge, it is the first time that a Simon task has been used in a fNIRS study. The oxygenation responses are consistent with previous neuroimaging studies reporting activity changes in the left PFC in cognitive tasks requiring selection and inhibition of information [46], as well as attentional monitoring [47]. It is often observed that the HbO_2 signal is characterized by higher signal amplitude than the HHb signal [48]. This was the case in the current study. Because HbO_2 is representative of the arterial compartment, it is more affected by systemic fluctuations than HHb which comes mostly from the venous compartment [35]. In addition, spatially resolved spectroscopy method is intrinsically more sensitive to the changes occurring in deep tissue layers, as compared with variables computed according to the standard modified Beer–Lambert law. Therefore, using measures of both changes in HHb and TOI might have reflected cortical activation better than changes in HbO_2 and Hbtot, prone to more systemic influences as encountered at high altitude [44].

Despite the low sample size of data, several important trends in cortical activation patterns during the Simon task are worth noting. As represented on Fig. 2A, the hemodynamic changes suggest that the magnitude of TOI and HHb responses were maximal during the early adaptation (D0 and D2) compared to D4. This suggests an initial (D0) pronounced engagement of the PFC that was maintained (D2) and then progressively reduced (D4) as participants adapted to high-altitude. These preliminary findings could support the differential involvement of the left prefrontal area during early and late adaptation to high altitude. One remaining question is whether these changes in PFC activity are related to the variations of the information processing efficiency observed during the sojourn at high-altitude.

Data from correlation analyses may help to better understand the relationship between the observed PFC hemodynamic changes and performance obtained in the conflict task. We observed moderate but significant relationships between RT variations and PFC oxygenation changes (HHb and TOI, respectively) during the first two days at altitude. More specifically, increased PFC activity coincided with faster RT. These results could be interpreted as a compensatory activation of a task-specific brain region leading to improved performance. PFC engagement appears beneficial during the transient phase (between D0 and D2). It may be less involved after four days of high altitude exposure following accommodation to hypoxia. The physiological mechanisms behind these observations remain unidentified. To summarize, the

present data suggests an adaptation of PFC activity to high altitude exposure in two phases, early and late. Nonetheless, it cannot be excluded that brain activity changes could also have occurred in some other brain regions that were not captured in this study.

Numerous studies over the past decade emphasized the important physiological consequences of high altitude exposure on the brain, regarding anatomy, cerebral blood flow, cerebral oxygenation and cortical excitability [49]. These brain hypoxic responses have been shown to be critical regarding altitude sickness on one hand and cerebral activation during exercise on the other hand [44]. Although neuropsychological functioning impairments at high altitude have been described for a long time, the effect of acute and prolonged hypoxic exposure on specific cognitive processes independently of the effect of intense physical activity (climbing) and changes in altitude levels (further ascent) remains to be clarified. Furthermore, the physiological cerebral correlates (e.g. cerebral perfusion and oxygenation) of altitude-induced changes in cognitive processes remain also to be elucidated. In this context, the present study provides important new insights regarding the specific changes in cognitive processes at high altitude and opens new perspectives regarding field assessment of neurophysiological mechanisms underlying changes in neuropsychological functions at high altitude. In this regard, fNIRS is a useful tool validated with other established neuroimaging techniques [50,51] which provides ecological assessment of hemodynamic changes in mental and motor testing [52]. While the present study involved a relatively small sample size due to logistic reasons, future studies involving larger sample size with additional measurements of brain response at altitude (e.g. EEG) are needed to confirm the present results and further elucidate the neuropsychological effects of high altitude exposure.

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