Dissociated Components of Executive Control in Acute Hypobaric Hypoxia

Endre Takács; István Czigler; Lívia Gabriella Pató; László Balázs

INTRODUCTION: The neurocognitive effects of acute hypobaric hypoxia are still largely unknown. This study was designed to test the hypothesis that executive control, an important component of cognition, is especially vulnerable to hypoxia.

- **METHODS:** Subjects participated in a simulated hypobaric chamber flight to 5500 m. Four auditory tasks were presented before, during, and after hypoxia: 1) Voice, and 2) Name variant of the Stroop task (both measuring conflict resolution); 3) go/ no-go task (GNG; measuring inhibition); and 4) two-choice reaction time task (CRT; which is a noninhibitory control task).
- **RESULTS:** The Stroop effect increased during hypoxia: in the Voice Stroop it increased from 49.4 to 83.6 ms for reaction time and from 4.1 to 12.3% for accuracy; in the Name Stroop from 43.5 to 82.9 ms for reaction time (accuracy remained unchanged). Accuracy declined from 82.3 to 75.0% in CRT, and from 85.8 to 77.5% (averaged over stimulus types) in the GNG task. Importantly, accuracy decreased similarly to go and no-go stimuli in the GNG task, revealing unaffected inhibition.
- **DISCUSSION:** The findings suggest that tasks requiring conflict resolution are more likely to be impaired than tasks requiring inhibition of response. Furthermore, our results provide evidence for the distinct nature of inhibitory control functions.

KEYWORDS: Stroop, go/no-go task, two-choice reaction time task, executive function.

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One important question concerns the particular vulnerability of executive functions¹⁴ and working memory,³ generally attributed to the frontal lobe.²⁹ Working memory is engaged in most cognitive processes during aviation, starting from spatial and numerical calculations to verbal communication. Executive functions are inevitable components of any purposeful, flexible behavior, and they are active during any time when "thinking outside the box" is necessary. Although these functions have been investigated repeatedly in hypoxia, there is still controversy as to whether these are the first to show impairments. For example, Phillips et al.²⁰ found no sign of impairment in Stroop conflict resolution. In cases when executive functions deteriorated in acute hypoxia, similar changes were detectable in almost every cognitive domain,^{25,26} together with a generalized slowing of reactions. Therefore, further investigations of executive functions in acute hypoxia are needed.

In a seminal study of executive functions Miyake et al.¹⁸ postulated three related, but separable executive control functions: shifting, updating, and inhibition. Two of the most commonly used measures of inhibitory executive control are the Stroop task and its variants¹⁷ and the go/no-go task (GNG).⁶ Taxonomies of inhibitory control functions offer classification for these tasks. Nigg's¹⁹ taxonomy separated GNG performance from abilities assessed by Stroop tasks. He labeled GNG behavioral inhibition, which is an ability to "suppress prepotent response"¹⁹ (p. 228). Stroop task performance was classified in

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the interference control factor. According to Nigg, interference control is necessary to "prevent interference due to resource or stimulus competition"¹⁹ (p. 228). In Stroop tasks the conflict arises from the competition between two aspects of a multifaceted stimulus. For example, in the classic color-word Stroop task the word information is dominant over color information owing to the automatic nature of reading skills. However, in GNG tasks there is no stimulus related conflict, as go and no-go stimuli are usually unambiguous and easily distinguishable perceptually from each other. Subjects must inhibit the motor response to no-go stimuli, even though it is the prevailing response as the frequent go stimuli require overt responses.

Both visual and auditory forms of these tasks are available. Although few studies have compared the auditory and visual forms of these tasks directly, they are believed to be equivalent. For example, Roberts and Hall²¹ showed that performance in visual and auditory Stroop variants is correlated and they activate comparable brain regions. The auditory Stroop task that Green and Barber¹² applied showed highly similar effects as the more frequently used visual Stroop tasks.

The main purpose of the current study was to investigate whether hypobaric hypoxia had different effects on these two aspects of inhibition, i.e., different effects on Stroop effect and on the results of a GNG task. Deficient conflict resolution would manifest as increased Stroop-effect, while problems with response inhibition in a GNG task would appear as a disproportionate increase of commission error (false alarm) rate in no-go trials compared to omission errors in go trials. At the outset we hypothesized that hypoxia would impair both aspects of inhibition, because both response inhibition (GNG) and conflict resolution (Stroop) are frontal functions.^{4,21,23} We assessed conflict resolution in voice-name Stroop-variant tasks and response inhibition in an auditory GNG task. As a noninhibitory control task, we introduced a two-choice reaction time task (CRT) with highly similar stimuli as the GNG task.

Acute hypoxia was induced by simulated flights in a hypobaric chamber. Cognitive performance was assessed by a within-subject design; measurements were accomplished before, during, and after hypoxic exposure.

METHODS

Subjects

Subjects were military jetfighter and helicopter pilots attending their compulsory annual checkup in the hypobaric chamber. The experiment was performed at the Aeromedical, Military Screening and Health Care Institute of the Hungarian Defense Forces, Kecskemét, Hungary. Subjects' vital functions were constantly monitored by a team of physicians and nurses. Subjects were 25 male pilots, between 25 and 52 yr of age (mean: 35.4, SD: 6.4). The sample consists of only male subjects because no female pilots appeared during the study period for hypobaric checkup. Due to technical problems, data from the GNG task from four subjects were omitted.

The study conformed to local ethics guidelines and the Declaration of Helsinki. Subjects participated voluntarily and

signed an informed consent prior to starting the experiment. Subjects were assured that their performance in these tasks would not affect their official evaluation, and their scores would only be accessible to the researchers for scientific purposes.

Materials

The following auditory tasks were presented: two versions of a Stroop-variant task, a CRT and a GNG task. In each task subjects responded with two buttons held in their left and right hands. Each task began with a short, prerecorded verbal instruction delivered through earphones.

In one of the Stroop-variant tasks, subjects had to respond to the gender of the presented names (Name Stroop task). In the other variant, the relevant aspect was the gender of the speaker (Voice Stroop task) (for similar auditory Stroop task, see Green and Barber¹²). The stimuli were 30-30 common Hungarian male and female names. All names were 350-400 ms long and had a loudness of 80 dB SPL. Every name was recorded by three distinct male and three female voices. This way the stimulus set consisted of 360 stimuli in total. In the Name-Stroop task, subjects had to respond with their right hand if they heard a male name, and with their left hand in case of a female name, irrespectively of the gender of the speaker. Conversely, in the Voice-Stroop task they had to push the right button if the gender of the speaker was male and the left button if female, irrespectively of the gender of the name. So, throughout the Stroop task, the mapping of gender to hands was constant (male - right hand, female - left hand), only the relevant aspect (name vs. voice) was varied. The duration of a trial was 1500 ms. In a block, 32 stimuli were presented. A block was approx. 1 min long.

In the CRT task subjects heard 100 ms long high (660 Hz) and low (440 Hz) pitched sounds, and they had to respond with the left or right hand to the low or high sounds, respectively. Stimuli were random and equally likely. In a block, 100 stimuli were presented, 50 high and 50 low pitch sounds.

In the GNG task, a similar set of stimuli was used as in the CRT task. High (70%) and low (16%) pitch sounds and missing sounds (14%) were interleaved. Subjects had to press both buttons upon hearing the high sound ("go" stimuli), but withhold their response when hearing the missing ("missing sound" stimuli) or the low ("no-go" stimuli) sound. Missing sounds were easily perceived as an abrupt break in the fast and repetitive sequence. In a block, there were 200 stimuli, 32 low sounds, 28 missing sounds, and 140 high sounds. Due to technical problems RT was not recorded for no-go commission errors. Both in the CRT and GNG task, the duration of a trial was 600 ms and an experimental block had duration of approx. 1 and 2 min, respectively.

We employed fast presentation rates (stimulus onset asynchrony or SOA of 600 ms) in the GNG and CRT tasks in order to increase the need for inhibitory control. This also helped to approximately equalize the difficulty of the four tasks.

Procedure

Subjects were tested in groups of 4-6 people. Arterial oxygen saturation (S_aO_2) was monitored by finger pulse oximetry (Hellige SpO₂ Sensor for Patient Monitor). Following a brief

familiarization with the tasks and stimuli, short practice sessions were presented (see **Fig. 1**). Afterwards, two blocks of preflight measurements (Stroop, CRT, GNG tasks) (Pre1 and Pre2) were obtained (altitude: 105 m, S_ao_2 range: 94–100%, average: 98.2%, SD: 1.2%). Upon completing these, the rapid ascent to 5500 m was accomplished in the hypobaric chamber. Five minutes after reaching the designated altitude, one block of stimuli from each task was completed (Hypoxia) (S_ao_2 range: 64–92%, average: 79.1%, SD: 6.0%). Shortly after returning to sea level altitude, subjects performed tasks one last time (Post) (S_ao_2 range: 91–100%, average: 96.8%, SD: 2.4%).

Statistical Analysis

The dependent variables were behavioral accuracy (in %) and median RT in each condition. Only reactions between 200 and 600 ms in the CRT/GNG tasks and between 200 and 1300 ms in the Stroop tasks were considered to be valid. In the GNG task, where both buttons had to be pressed simultaneously, RT was calculated by selecting the RT of the faster hand.

Normoxic baseline was calculated as the average of Pre1, Pre2, and Post blocks. This averaging helped us to eliminate the confounding practice effect that was apparent in most tasks. Repeated measures ANOVAs and dependent samples *t*-tests were conducted on RT and accuracy data.

In the analysis of Stroop tasks we first performed *t*-tests comparing compatible and incompatible trials during normoxia in order to check whether these Stroop variants produce reliable Stroop effects. Results in the Stroop tasks were then analyzed with ANOVAs using within-subject factors of BLOCK (Normoxia, Hypoxia), and COMPATIBILITY (compatible, incompatible). In the analysis of the CRT task and the RT analysis of the GNG task we also applied *t*-tests. The accuracy in the GNG task was analyzed with repeated measures ANOVA with BLOCK (Normoxia, Hypoxia) and STIMULUS ("missing sound", "no-go", "go") factors.

As an effect size estimate we report partial eta squared (η_p^2) for *F*-tests and eta squared (η^2) for *t*-tests. Post hoc follow-up comparisons were Bonferroni-corrected.

RESULTS

Voice Stroop Task

The analysis of RT (**Fig. 2A**) revealed a nonsignificant main effect of BLOCK [F(1,24)=3.80, P = 0.06, $\eta_p^2=0.10$]. The COMPATIBILITY main effect was significant [F(1,24)=22.57,

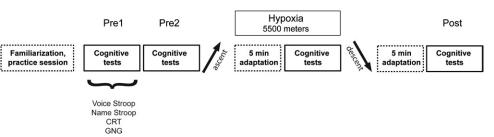


Fig. 1. Testing paradigm.

P < 0.0001, $\eta_p^2 = 0.48$], revealing that there was a significant Stroop-effect throughout the experiment. The interaction between BLOCK and COMPATIBILITY factors was also significant [F(1,24)=4.42, P < 0.05, $\eta_p^2 = 0.16$], reflecting an increased Stroop effect in hypoxia. In the normoxic baseline the RT advantage of compatible trials was 49.4 ms (SD: 51.9 ms), in hypoxia 83.6 ms (SD: 102.1 ms).

The ANOVA on accuracy (**Fig. 2B**) showed a significant BLOCK main effect [F(1,24)=7.57, P < 0.05, $\eta_p^2=0.24$], demonstrating that subjects were generally more error prone in hypoxia than during baseline. We obtained a significant COM-PATIBILITY main effect [F(1,24)=15.23, P < 0.001, $\eta_p^2=0.39$]. The BLOCK × COMPATIBILITY interaction was also significant [F(1,24)=4.96, P < 0.05, $\eta_p^2=0.17$], which reveals that the Stroop-effect was larger in hypoxia than in normoxia. In normoxia the accuracy advantage of compatible trials was 4.1% (SD: 6.3%), in hypoxia 12.3% (SD: 18.6%).

Name Stroop Task

The analysis of RT (**Fig. 3A**) showed a nonsignificant main effect of BLOCK [*F*(1,24)=1.69, *P* = 0.21, η_p^2 =0.07]. The significant COMPATIBILITY main effect [*F*(1,24)=56.75, *P* < 0.00001, η_p^2 =0.70] revealed a strong Stroop-effect all through the blocks. The interaction between the BLOCK and COM-PATIBILITY factor was also significant [*F*(1,24)=4.96, *P* < 0.05, η_p^2 =0.17], demonstrating increased Stroop-effect in hypoxia. Compatible trials showed 43.5 ms (SD: 34.0 ms) RT advantage compared to incompatible trials in the normoxic baseline and 82.9 ms (SD: 79.3 ms) in hypoxia.

The ANOVA on accuracy demonstrated a significant main effect of BLOCK [F(1,24)=4.49, P = 0.05, $\eta_p^2=0.16$] (**Fig. 3B**), reflecting generally lower accuracy in hypoxia. The COMPATI-BILITY main effect was also significant [F(1,24)=16.35, P < 0.001, $\eta_p^2=0.41$], which was due to the significant Stroop-effect throughout the experiment. The interaction between factors, however, was nonsignificant [F(1,24)=2.11, P = 0.16, $\eta_p^2=0.08$], meaning that in this task Stroop-effect in accuracy was unchanged during hypoxia (accuracy advantage of compatible trials in normoxia: 3.6% (SD: 5.5%), in hypoxia: 6.8% (SD: 10.5%)).

CRT Task

Fig. 4A shows RT in the CRT task. The dependent samples *t*-test revealed no difference between baseline and hypoxia $[t(24)=0.70, P=0.49, \eta^2=0.02]$.

However, in the analysis of accuracy in the CRT task, we obtained significant difference between baseline and hypoxia

> [$t(24)=3.65, P < 0.01, \eta^2=0.36$)] (**Fig. 4B**), revealing diminished accuracy in hypoxia.

GNG Task

Reaction time to "go" stimuli in the GNG task was unaffected by hypoxia (**Fig. 5A**), as revealed by the nonsignificant *t*-test (t(20)=0.52, P=0.61, $\eta^2=0.01$).

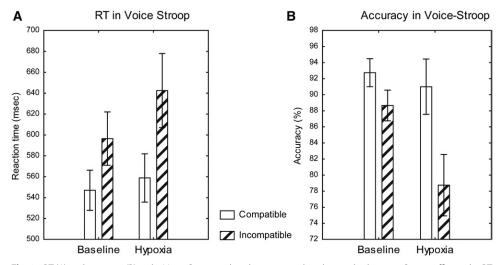


Fig. 2. RT (A) and accuracy (B) in the Voice Stroop task in the normoxic baseline and in hypoxia. Stroop effect – the RT and accuracy advantage of compatible compared to incompatible trials – increased significantly during hypoxia both in RT and accuracy. Error bars represent SEM.

In the accuracy analysis (**Fig. 5B**) we tested if hit rate in go trials (100% minus omission errors) changed differently in hypoxia than in no-go ("missing sound" and "no-go") trials (100% minus commission errors). The main effect of BLOCK was significant [F(1,20)=20.23, P < 0.001, $\eta_p^2=0.50$], revealing generally lower accuracy in hypoxia. The main effect of STIMULUS [F(2,40)=32.08, P < 0.00001, $\eta_p^2=0.62$] was further examined with post hoc Bonferroni tests, which indicated that accuracy to "no-go" stimuli was lower than to other stimuli (P values < 0.00001 in both cases, df = 20).

The interaction between BLOCK and STIMULUS factors was also significant [F(2,40)=3.67, P < 0.05, $\eta_p^2=0.16$]. First we checked whether the STIMULUS main effect was modulated by BLOCK. Therefore, we applied Bonferroni corrected *t*-tests between the three types of stimuli both in normoxia and hypoxia (9 comparisons together with the next analysis, critical P = 0.0056). In both cases, the patterns of results were

similar: "no-go" accuracy was significantly lower than "missing sound" or "go" accuracy, but in hypoxia the "missing sound" vs. "go" comparison also reached significance [t(20)=3.62, P = 0.0017, $\eta^2=0.40$].

The other possibility behind the interaction is that BLOCK main effect is modulated by the STIMULUS factor. Bonferroni corrected *t*-tests indicated that accuracy decreased significantly in hypoxia in "go" [t(20)=3.41, P = 0.0028, $\eta^2=0.37$], and "nogo" trials [t(20)=3.52, P =0.0022, $\eta^2=0.38$], but not in "missing sound" trials [t(20)=2.55, P = 0.019, $\eta^2=0.25$, ns]. The BLOCK*STIMULUS interaction

therefore might be caused by the weaker effect of hypoxia on accuracy in the "missing sound" trials. Most importantly for the main hypothesis of the study, this accuracy drop was not larger than the accuracy drop in "go" trials.

DISCUSSION

Fast ascent to 5500 m and concomitant drop in $S_a o_2$ resulted in impairments of behavioral accuracy in all investigated tasks. It is a well-established result that moderate and severe acute hypoxia leads to generalized slowing in relatively simple reaction time tasks^{7–10,15} (for review see Virués-Ortega et al.²⁹). In the present study we obtained diminished accuracy both in the GNG and CRT task in hypoxia. It is an interesting finding that in the GNG and CRT tasks performance impairment appeared in accuracy but not in RT. This might be due to the rapid pre-

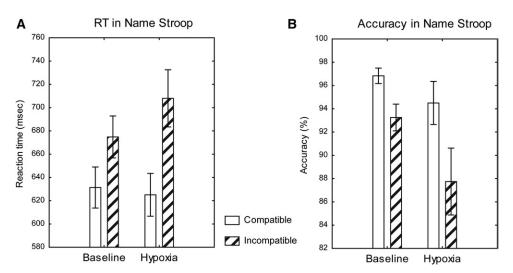


Fig. 3. RT (A) and accuracy (B) in the Name Stroop task in the normoxic baseline and in hypoxia. Stroop effect increased significantly during hypoxia only in RT.

sentation rate (SOA 600 ms) that required very fast responses and subjects sacrificed accuracy for speed. Therefore, the basis of this impairment in accuracy might be similar to that of the generalized slowing in the abovementioned studies. We also observed diminished accuracy in the Stroop tasks, which supports the notion that acute hypoxia causes widespread cognitive problems.²⁵

Our auditory name-voice Stroop tasks evoked robust and significant Stroop effects both in RT and accuracy. Unlike the classic color-word Stroop,¹⁷ the interference was symmetrical, both the gender of the name

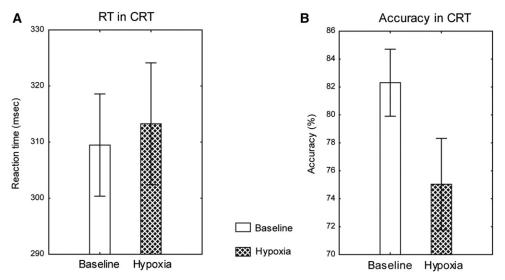


Fig. 4. Mean reaction time (A) and accuracy (B) in the CRT task. RT remained unaffected; accuracy decreased in hypoxia.

interfered with the gender of the voice and vice versa. A similar symmetric Stroop effect was found by Green and Barber¹² (Experiment 3) in a comparable auditory paradigm.

In hypoxia, Stroop effect increased in both Stroop variant tasks, and in the Voice Stroop task; this increased interference was significant in RT and also in accuracy. In the GNG task, accuracy also decreased during hypoxia, but similarly in commission errors (false alarms) in "no-go" trials and in omission errors in "go" trials; the accuracy decrease in the other no-go stimuli ("missing sound") was not significant. Therefore, we can conclude that hypoxia did not impair inhibitory executive functions in general, only conflict resolution measured by the Stroop tasks was compromised, whereas response inhibition in the GNG task remained unaffected.

Previously, response inhibition in GNG tasks was investigated sparsely in hypobaric hypoxia. While Kida et al.,¹⁵ in an auditory study, did not obtain selective impairment in no-go response accuracy, Tsarouchas et al.,²⁴ in a visual study, did. However, the comparability of these studies might be limited, since demands of inhibition were different due to different event presentation rates (SOA:¹⁵: 2000 ms,²⁴: ~1500 ms, present study: 600 ms), no-go stimulus probability (80%, 50%, 30%, respectively), and task stimuli.

There is substantial controversy in the literature regarding the impact of moderate acute hypoxia on the Stroop effect. Asmaro et al.¹ reported impaired performance in a visual colorword Stroop task in the 7620 m condition, but not in the 5334 m condition. Unfortunately, the method they adapted did not allow separation of the genuine

Stroop effect from generalized slowing. In an acute normobaric study using a 10% oxygen gas mixture, an approximate altitude equivalent of 5500 m, the visual color-word Stroop effect in RT was even attenuated.²⁶ This effect was not directly assessed by the authors; it is our calculation from the raw data available in the supplementary material. The authors used the CNSVS test battery,¹³ where compatible and incompatible RT was measured in different blocks with slightly different tasks. In one block of trials the task was to press the spacebar if the color of the ink and word matched, and in the other block if the color of the ink and word were mismatched. The RT difference between these blocks are supposed to reflect the Stroop effect, but in our view it might as well reflect the fast-same effect¹⁶ or a combination of these effects. In another normobaric study subjects were exposed to 5486 m simulated altitude.²⁰ Authors employed a visual number Stroop task and obtained no impairment. In sum, no study found reliable change in Stroop effect in the 5000-6000 m altitude range to date. These studies used different

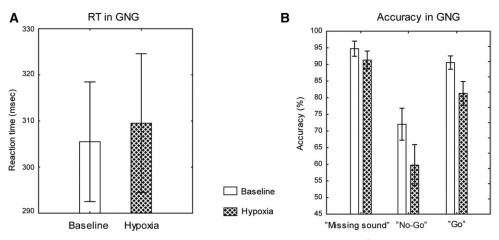


Fig. 5. Mean reaction time (A) and accuracy (B) in the GNG task. RT remained unaffected, accuracy decreased in hypoxia. The accuracy decrease was significant in "no-go" and "go" trials, but not in "missing sound" trials.

versions of the Stroop task which might be in part responsible for the diverse results. However, further studies are necessary to reveal the exact source of this discrepancy.

The dissociation of response inhibition (GNG task) and conflict resolution (Stroop effect) in hypoxia argues against a unitary phenomenon of inhibition.²⁸ Further challenge to this view comes from studies revealing differential vulnerability of these abilities in neurological damage (traumatic brain injury⁵). Still, the study of Friedman et al.¹¹ provides evidence that response inhibition and conflict resolution correlates at least moderately. So the question arises: do Stroop and GNG tasks measure a common inhibitory activity or not?

It is very likely that there are both common and unique mechanisms, as well. The present results could be interpreted as hypoxia impaired those mechanisms (or cortical areas) that are unique to Stroop. For example, fMRI imaging studies show overlapping, but not identical neural sources of response inhibition and conflict resolution. A meta-analytic study of colorword Stroop fMRI experiments identified several clusters of activation in the frontal and insular cortex.⁴ In addition, a systematic review has reported that conflict tasks (e.g., Stroop) activate the anterior cingulate cortex, bilateral prefrontal cortex, insula, and the parietal lobe.²¹ These areas were also active when they subsequently tested subjects with an auditory variant of Stroop.²¹ As for response inhibition, in an fMRI metaanalysis²³ authors obtained activation in simple GNG tasks in the right presupplementary motor area (pre-SMA), bilateral occipital regions, and the precuneus (the medial part of the superior parietal cortex). Thus, simple GNG tasks, like the one used in the present study, activate primarily the pre-SMA in the frontal cortex, while Stroop tasks activate a broader frontal network. The lack of impairment in response inhibition in the GNG task may indicate that only certain areas of frontal cortex (but not the pre-SMA) are especially sensitive to hypoxia.

An alternative explanation for the dissociation of Stroop and GNG performance is related to processing stages. Although the existence of distinct processing stages is a controversial issue, ²² some researchers^{11,30} share the view that inhibition in the Stroop and GNG task operates in different information processing stages. Specifically, inhibition in Stroop tasks operates in both stimulus and response related processing stages, from relatively early till late stages.²⁷ In contrast, in response inhibition is present only in late stages, related to motor output.³⁰ We therefore speculate that the current results indicate that hypoxia impaired processing stages before motor output, since GNG inhibitory performance remained intact.

It is not a new result that generalized slowing (or generalized performance decrement) occurs in acute hypoxia at this altitude. It undoubtedly affects the safety of every operation, therefore in aviation every effort should be made to prevent it. The results of the current study support the idea that certain aspects of executive control might be impaired as well. Executive functions are especially important in unusual situations where one must override learned, habitual responses. In aviation hypoxic exposures could happen during emergencies (e.g., explosive depressurization due to accident or flight instrument failure), when aircraft personnel must find new solutions to control the situation. In cases such as these, erroneous signals must be recognized and overridden.

However, it must be kept in mind that although the theoretical importance of executive functions is clear in cognitive psychology, task paradigms used in basic research are often difficult to translate to everyday situations. It is especially true for the Stroop task. Therefore these results should only be starting points for further research and cautious interpretation is advised.

In the current study the subject sample was quite specific: male military jetfighter and helicopter pilots. They were selected through rigorous and competitive physical, cognitive and psychological entrance examinations. They were currently carrying a pilot license and had been exposed to hypoxic testing repeatedly in the past. Therefore, our subjects cannot be considered normal, everyday subjects, thus any generalization of these results to the larger population must be made cautiously. However, the two most significant fields where hypobaric hypoxia constitutes danger are aviation and mountaineering. Thus, the given subject sample can be regarded as adequate. As another consequence of this specific sample, the present results most probably underestimate the effect that hypoxia would have on naïve civilians. Moreover, due to ethical and safety reasons civilians cannot be exposed to such levels of hypobaric hypoxia in many countries.

Another limitation of the study might be the absence of a placebo control group. The main reason for that – apart from organizational constraints – is that simulated flights in a hypobaric chamber cause distinctive physical symptoms (shortness of breath, ear fullness) which are absent in placebo flights. Therefore, subjects who previously experienced a fast ascent in the hypobaric chamber would always be aware that they are participating in a placebo flight.

In conclusion, moderate-severe acute hypobaric hypoxia impaired cognitive functions considerably, especially executive functions responsible for conflict resolution. The differential response of GNG and Stroop task indicates that the effect of hypoxia on inhibitory executive functions is not uniform, but depends on the processing requirements of the task paradigms. Further research using executive control tasks is necessary to achieve a better understanding of cognitive impairments in response to acute hypoxia.

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