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Impact of acute hypobaric hypoxia on blood flow distribution in brain

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Abstract

Aim: Acute hypobaric hypoxia is well known to alter brain circulation and to cause neuropsychological impairment. However, very few studies have examined the regional changes occurring in the brain during acute exposure to extreme hypoxic conditions.

Methods: Regional cerebral blood flow (rCBF) response to hypoxia was investigated in six healthy subjects exposed to either normobaric normoxia or hypobaric hypoxia with ambient pressure/inspired oxygen pressure of 101/21 kPa and 50/11 kPa respectively. After 40 min at the desired pressure they were injected ^{99m}Tc-HMPAO and subsequently underwent single photon emission computed tomography. Regional cerebral blood flow distribution changes in the whole brain were assessed by Statistical Parametric Mapping, a well established voxel-based analysis method.

Results: Hypobaric hypoxia increased rCBF distribution in sensorymotor and prefrontal cortices and in central structures. PCO_2 correlated positively and $SatO_2$ negatively with rCBF in several temporal, parahippocampal, parietal and central structures.

Conclusions: These findings underscore the specific sensitivity of the frontal lobe to acute hypobaric hypoxia and of limbic and central structures to blood gas changes emphasizing the involvement of these brain areas in acute hypoxia.
Keywords frontal lobes, hypobaric hypoxia, limbic system, rCBF, SPECT, SPM.

Increase of cerebral blood flow (CBF) during altitude exposure and hypoxia is mediated by blood and endothelial factors (Pearce 1995). This vasodilatation is partly counteracted by hyperventilation-induced hypocapnia (Brugniaux *et al.* 2007) even if the effect of hypoxaemia is generally dominant in normal subjects. Little is known whether these changes are uniform across all brain regions. The effect of acute hypoxia on cerebral hemodynamics has been mostly investigated using hypoxic gas mixtures under normobaric conditions and the relatively few investigations on regional cerebral blood flow (rCBF) have reported inconclusive results (Buck *et al.* 1998, Binks *et al.* 2008).

Recent studies on memory have shown the important role of frontal lobes, not only in storing information but also in their recall (Budson & Price 2005). In particular, frontal lobes seem to play a critical role in the repositing of temporal information which is required to place any event into its context (Squire 1987). Pagani *et al.* (1998) submitted a memory test to climbers at an altitude of 5350 m before and after acclimatization. The main finding was a more marked detrimental effect for organization than for information storage before acclimatization and results were interpreted as a more marked effect of the acute hypoxia on frontal lobes.

In a previous study (Pagani *et al.* 2000) we investigated rCBF in six healthy subjects in a hypobaric chamber, reproducing the ambient conditions at 5500 m above sea level (a.s.l.). This permitted exposure to hypobaric hypoxia, closely reflecting the actual acute state faced at high altitude, i.e. helicopter or fast ascents by cable cars, and yet minimized both mental stress and individual physiological variability. Forty minutes after reaching hypoxic condition the subjects were injected with a radiotracer whose uptake was proportional to cerebral perfusion and subsequently underwent single photon emission computed tomography (SPECT) to assess rCBF distribution changes as compared to the normoxic state. Three-dimensional standardization software identified and analysed pre-determined volumes of interest (VOIs) on a limited number of brain regions, based on the relevant literature on the effects of hypoxic state on brain. Hypobaric hypoxia resulted in a relative rCBF increase in primary motor cortex and basal ganglia (Pagani *et al.* 2000).

Our previous report is still the only one assessing functional rCBF changes in acute hypobaric hypoxic conditions by SPECT. Functional studies have seldom been discussed in respect to possible neurocognitive deficits. This potential link merits more attention, especially considering executive functions, such as perception, memory and codification, shown to be impaired by hypoxia (Virués-Ortega *et al.* 2004). In the present study we have investigated the same brain SPECT data under a different perspective by implementing Statistical Parametric Mapping (SPM), which allowed us to enlarge the analysis to the whole brain, to correlate CBF to physiological parameters and to look for finer focal changes in grey matter, particularly in frontal and temporal lobes.

Materials and methods

Subjects

Four males and two females (mean age 34 ± 8), all right-handed and with normal brain at magnetic resonance imaging (MRI), were investigated. Both Ethical and Isotope Committees of the Karolinska University Hospital approved the study and each subject gave her/his informed consent to the experiment.

Chamber and camera measurements

The detailed methodology of the study has been published in the previous investigation (Pagani *et al.* 2000). Briefly, each participant was exposed in a hypobaric chamber to normobaric normoxia or hypobaric hypoxia with ambient pressure/inspired oxygen pressure of 101/21 kPa and 50/11 kPa, respectively, on two separate occasions. A portable device monitored electro-cardiogram, peripheral haemoglobin saturation ($SatO_2$) and non-invasive blood pressure. Subjects were breathing air through a mask, without chamber pressure change during normoxia. For the hypoxia branch, chamber pressure was reduced by 100–110 Pa s^{-1} to reach a level of 50 kPa in 8 min.

A dose of 330 MBq of ^{99m}Tc-D,L-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO, CERETEC®; Amersham International plc, Little Chalfont, Amersham, UK) was injected after 40 min at the desired hypoxic level. Since the experiment was performed within the chamber with an experimental protocol relatively long in time, ^{99m}Tc-HMPAO was stabilized with methylene blue to allow administration up to 4 h after preparation, according to the manufacturer's instructions. In all cases, administration of radiopharmaceutical was made between 33 and 236 min after its preparation. In the hypoxia branch arterial blood samples were taken 5 min after the radiotracer injection to assess partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2), pH and $SatO_2$. In the normoxic arm of the experiment invasive arterial blood gases were not taken for ethical reasons assuming normative values in healthy resting individuals. At the end of the experiment the subjects returned to normobaric room air and SPECT was performed in a next-door laboratory at the Karolinska University hospital within 30 min from arrival at normobaric conditions using a three-headed gamma camera. ^{99m}Tc-HMPAO reaches its final distribution about 1 min after injection, then fixates into the brain cells and remains stable for several hours. Within this period, the images from the scan will depict those regions activated at the time of distribution and fixation. The exact timing of the SPECT scan, provided it is long enough to allow a sufficient number of photons to be detected (22.5 min in the present experiment), is therefore not relevant if it is performed within 3 h from injection.

The projection data was pre-processed using a 2D Hamming filter, reconstructed by filtered back projection and corrected for attenuation. Both acquisition and reconstruction were performed in 128×128 matrices with a voxel size of 2.22×2.22 mm^2.

SPM analysis

Voxel-based analysis was performed using the 2000 version of SPM (SPM2, Wellcome Department of Cognitive Neurology, London, UK). Images of relative tracer distribution were spatially normalized to a pre-defined SPECT template (voxel size $2 \times 2 \times 2$ mm) using a 16-parameter affine (non-linear) transformation. Images of relative tracer distribution were spatially normalized in the stereotactic Montreal Neurological Institute space

to a pre-defined SPECT template. Correction of SPM coordinates to match the Talairach coordinates was achieved by the subroutine implemented by Brett *et al.* (2001). Brodmann areas (BAs) were then identified, after importing the corrected coordinates, (http://www.talairach.org/index.html) at a range of 0–2 mm from the Talairach coordinates resulting from the SPM output isocenters.

After global normalization, images were smoothed with a Gaussian filter (10 mm) to account for individual gyral differences and brain anatomy, also taking into consideration the spatial resolution of the SPECT camera (11 mm FWHM). Images were globally normalized using proportional scaling to remove confounding effects due to global CBF changes, with a threshold masking of 0.8.

The voxel-based analyses were performed using a 'two conditions: one scan/condition, paired *t*-test' design model, and significances were sought for the contrasts between normoxic and hypoxic conditions. Correlations were computed between the ^{99m}Tc-HMPAO retention in hypoxic conditions and $SatO_2$, PO_2 and PCO_2 using the 'single subject: covariates only' routine of SPM2 with the blood gases scores as covariates of interest. Significant differences between the two conditions were set at a height threshold of $P = 0.01$, corrected for multiple comparison at cluster level ($P_{corrected} < 0.0001$), and the threshold at voxel level was set to $P < 0.0001$. The height threshold for the correlation analyses was $P = 0.05$, corrected for multiple comparison at cluster level ($P_{corrected} < 0.005$), and the threshold at voxel level was $P < 0.0001$. Only clusters containing more than 100 voxels were considered to be significant. This was based on the calculation of the partial volume effect resulting from the spatial resolution.

Results

During hypobaric hypoxia there were no signs of mental stress. A high variability was found in arterial blood gases with PO_2 ranging between 3.19 and 4.63 kPa (mean 3.73 ± 0.53), PCO_2 between 4.38 and 5.53 kPa (mean 4.53 ± 0.67) and $SatO_2$ between 43 and 71% (mean 56 ± 11). Simultaneously measured pulse oxymetry $SatO_2$ values (mean 53%) corresponded to the arterial ones. The $SatO_2$ time course was curvilinear and steady state was not seen until approx. 30 min after reaching 50 kPa hypobaric ambient pressure (Fig. 1). Respiratory rate decreased from 13.8 to 7.6 breaths per minute and heart rate increased from 63 to 86 beats min^{-1} during hypoxia as compared to normoxia. Blood pressure remained unchanged.

In acute hypobaric hypoxia, as compared to the normoxic condition, significantly higher ^{99m}Tc-HMPAO distribution was found in the right temporal lobe (BA 20) and anterior cingulated cortex (BA 32) as well as in bilateral sensorymotor cortex (BAs 3, 4 and 6), prefrontal cortex (BAs 9, 10 and 45) and basal ganglia (Fig. 2). Sparse white matter regions in the vicinities of all the reported regions were found at 1 mm from the transformed isocenters.

Highly significant positive correlations with PCO_2 were shown in the left putamen and amygdala and anterior cingulate cortex, the right orbitofrontal cortex (BA 47) and inferior parietal lobule (BA 40) and bilaterally in the temporal lobe (BAs 21, 22 and 38) and in the parahippocampal gyrus (BAs 34, 35 and 36) (Fig. 3). Negative correlations with $SatO_2$ were found for rCBF distribution in left thalamus and substantia nigra, in right insula (BA 13) parietal cortex (BAs 40 and 37), orbitofrontal cortex (BA 47), amygdala and hippocampus and bilaterally in temporal cortex (BAs 20, 21, 22 and 38) and parahippocampal cortex (BAs 28, 34, 35 and 36) (Fig. 4).

In both latter analyses significances at the chosen threshold were limited to grey matter. No significant correlation between rCBF and PO_2 was found at the chosen statistical threshold. However, a trend towards a negative correlation with CBF distribution was found in the most of the regions in which CBF negatively correlated with PCO_2.

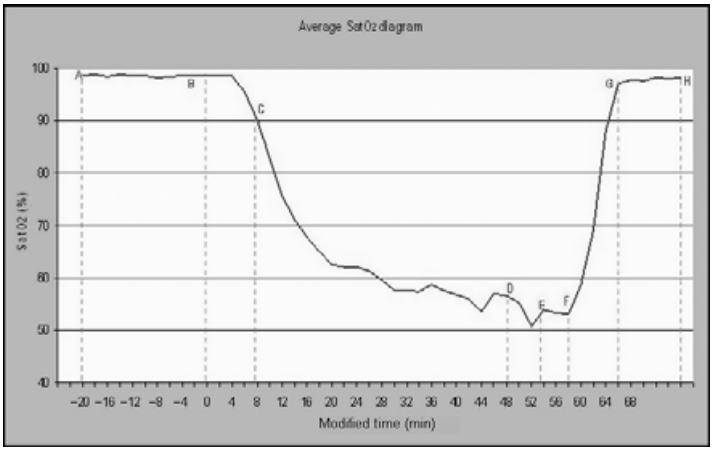

Figure 1 Average $SatO_2$ time course in hypobaric experiment from chamber closing (A) until opening (H). Zero time (B) marks beginning of depressurization. Steady state was seen approx. 30 min after arrival (C) at 50 kPa pressure. Radiotracer injection (D) and arterial blood sampling (E) were performed before pressurization (F–G).

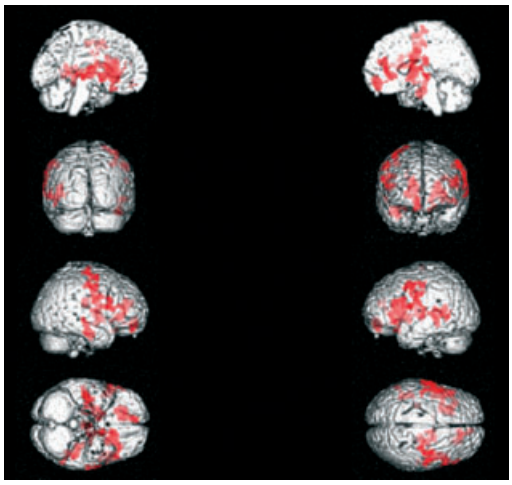

Figure 2 Three-dimensional rendering of voxels reflecting significantly higher brain perfusion distribution during hypobaric hypoxia as compared to normobaric normoxia. The height threshold was set at $P = 0.01$; P was <0.0001 at corrected cluster level; at voxel level the uncorrected P was <0.0001 and the z-score ranged between 4.52 and 4.15 for the various clusters (cluster size between 534 and 1590 voxels).

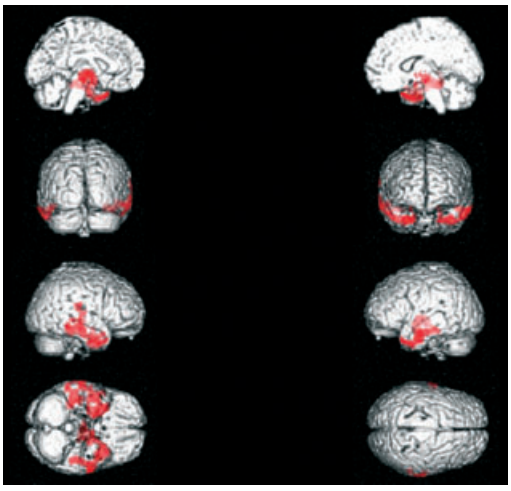

Figure 4 Three-dimensional rendering of voxels reflecting a significant negative correlation between $SatO_2$ and rCBF during hypobaric hypoxia. The height threshold was set at $P = 0.05$; P was <0.005 at corrected cluster level; at voxel level the uncorrected P was <0.0001 and the z-score of the two clusters were 4.67 and 3.87 (cluster size 1758 and 1617 voxels respectively). rCBF, regional cerebral blood flow.

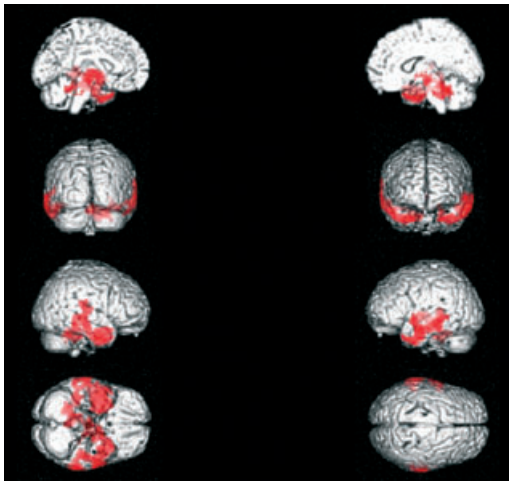

Figure 3 Three-dimensional rendering of those voxels reflecting a significant positive correlation between PCO_2 and rCBF during hypobaric hypoxia. The height threshold was set at $P = 0.05$; P was <0.0001 at corrected cluster level; at voxel level the uncorrected P was <0.0001 and the z-score was 4.36 and 4.22 for the two clusters (cluster size 3347 and 3062 voxels respectively). PCO_2, partial pressure of CO_2; rCBF, regional cerebral blood flow.

Discussion

The present investigation confirmed the findings of an increased ^{99m}Tc-HMPAO distribution in motor cortex and basal ganglia under hypobaric hypoxia, as previously assessed by VOIs analysis (Pagani *et al.* 2000). The implementation of voxel-based analysis by SPM improved substantially the quality and reliability of the results and provided more relevant information, as large clusters of voxels were found to be significantly different between hypobaric and normobaric condition. This made it possible to find significant, previously undetected, rCBF changes in the sensorymotor, pre-motor and dorsolateral prefrontal cortex as well as in temporal and anterior cingulate cortices.

The administration of the radiopharmaceutical was performed 40 min after reaching hypobaric hypoxia at a quite severe acute hypoxic level (Fig. 1). The uptake in the brain of ^{99m}Tc-HMPAO reaches a plateau about 2 min after injection and is almost stable for the following 3–4 h. Since the SPECT images were taken within 30 min after injection, the results of this study reflected the distribution of the perfusion-related compound in the brain during the acute hypoxic state.

Using functional neuroimaging and systematically investigating the perfusion changes that take place in the whole brain with a spatial resolution of about a centimetre, the present investigation highlighted the larger rCBF distribution in the forebrain grey matter, confirming the occurrence of selective regional changes during acute hypoxia. This localized response may be tentatively ascribed to an acute compensatory mechanism involving regions more sensitive to oxygen deficit which would possibly develop a reversible neuronal impairment during a phase of acute hypoxia.

Inconclusive results have been reported in investigations on rCBF response to acute hypoxia. In a recent study using arterial spin labelling MRI, Dyer *et al.*

(2008) studied rCBF during mild acute normobaric hypoxia breathing 12.5% oxygen ($SatO_2$ 89%). They reported a proportionally equal rCBF increase in grey and white matter without differences between brain regions. Buck *et al.* (1998) used PET with ^{15}O-H2O on eight healthy volunteers exposed to consecutive 20 min periods of mild to moderate normobaric hypoxia corresponding to altitudes of 3000 and 4500 m. By using SPM they found a significant increase of blood flow in the hypothalamus. A smaller increase was also found in the thalamus. These rCBF changes were seen only under the most intense hypoxic provocation where mean PO_2 was 5.5 kPa. Our discrepant results may be due to the more severe hypoxia, as well as the hypobaric state, provoked in our controlled experimental setup (mean PO_2 3.73 kPa).

In a PET study following 63 days at altitudes up to 6157 m, Hochachka *et al.* (1999) found metabolic reductions in frontal lobes. In another PET study Binks *et al.* (2008) reported changes in blood flow localized in the 'older brain, possibly to maintain essential homeostatic functions, even at the cost of reduced cognitive function'.

The attempt to reproduce the closest-to-natural high-altitude conditions seems nowadays particularly appropriate, since a specific response to hypobaric hypoxia differing in magnitude and quality from the one to normobaric hypoxia has recently been reported. Savourey *et al.* (2003) exposed 18 subjects to a 40 min test, the same duration as in our experiment. Hypobaric hypoxia led to a greater hypoxaemia, hypocapnia, blood alkalosis and a lower $SatO_2$. These findings imply that investigations aiming to study cognitive and pathologic (i.e. acute mountain sickness) changes have to take the barometric variable into account.

Furthermore, if PCO_2 variability is taken under control and hypoxia is induced by a gas mixture inhaled through constrictive masks this might cause psychological and physical discomfort, affecting brain functions and other physiological responses.

Neuropsychological and neurobehavioral malfunctioning have often been reported in acute as well as in chronic exposure to hypoxia. Neurophysiological activity and cognitive functions such as memory, learning and attention have been reported to be affected by mild and severe hypoxia (Virués-Ortega *et al.* 2004).

Damage to the dorsolateral prefrontal cortex, BAs 10 and 45, found to be implicated in the response to hypoxia in the present study is known to cause cognitive deficits (Fuster 1997, Steele & Lawrie 2004) and the segregation of cognitive and emotional functions in the medial frontal cortex has also been described (Bush *et al.* 2000). Alterations in abstract reasoning and verbal fluency (Petiet *et al.* 1988) as well as grammatical reasoning (Kennedy *et al.* 1989) were also found during severe hypobaric hypoxia. Regard *et al.* (1989) reported an impaired cognitive flexibility in climbers, resulting from the analysis of verbal fluency related tests, evaluated months after their latest ascent. Similarly did Van Diest *et al.* (2000) in controlled mild hypoxic laboratory conditions. Subjects exposed to various altitudes ranging from 5488 to 8848 m a.s.l. worsened in verbal long memory and aphasia screening test 1 month after exposition (Hornbein *et al.* 1989). Overall these findings underline a clear impairment of high processes, executive tasks, verbal fluency and abstract reasoning making during hypoxia. This points towards the prefrontal lobe as one of the regions most prone to physiological and neuropsychological changes in such ambient conditions.

Attention has been largely recognized as due to at least two distinct network systems. The dorsal network includes the frontal eye field and the superior parietal cortex while the ventral one consists of the lateral and inferior frontal/prefrontal cortex and of the temporo-parietal junction (Corbetta & Shulman 2002). The first system seems to be stimulus driven and the second task oriented. Recently Fox *et al.* (2006) found that both systems are also active under resting conditions, i.e. in the absence of any stimulus or task demand, suggesting some independence from other systems, like sensory or motor systems (Luo *et al.* 2010). It is worth noting that some of the areas implicated in the attention networks, particularly the ventral one, have been shown by our results to be affected by acute hypoxia. This is not surprising since attention, a basic process of the brain, is oxygen- and energy-consuming and acute hypoxia causes a fundamental slowing of neuronal processing. We can speculate that in the very acute phase of hypobaric hypoxia some central mechanism may control and modulate blood flow to regions implicated in attention in order to avoid immediate mishaps in a potentially dangerous ambient condition.

Another finding of the study was that rCBF was highly correlated to both $SatO_2$ and PCO_2 in limbic structures such as bilateral temporal lobes and parahippocampal gyrus. These results are difficult to be interpreted, also due to the lack of previous analogous investigations, but suggest that the local regulation of vascular tone in these regions is somewhat different than in other brain areas.

The selective vulnerability of specific brain regions to hypoxia and carbon dioxide levels might be due to several local factors as the specific biochemical and metabolic characteristics of different structures, their anatomical position and vulnerability, their blood supply and their different response over time (Kuroiwa & Okeda 1994, Caine & Watson 2000). During acute hypobaric hypoxia, as in our experiment, this last factor might have accounted for the early response to subtle

neuronal sufferance in regions with higher need of oxygen supply due to increased metabolic demand (Moody *et al.* 1990, Hornbein 2001).

In the long run, such hypoxia could result in chronic structural and functional changes. In this respect White *et al.* (1984) speculated about an initial hyperperfusion in hypoxia followed by a progressive increase in small-vessels resistance, resulting in lower perfusion rates and neuronal damage.

Moreover, in hypobaric hypoxia, psychomotor effects of altitude have also been reported, especially alterations in motor speed (Peña-Casanova *et al.* 1997, Bolmont *et al.* 2000). Atrophy in motor-related cortical regions has been described in high-altitude climbers in BAs 4 and 6, in which we found a larger response to acute hypobaric hypoxia. Persistence of motor impairment has also been detected a long time after return to sea level (Di Paola *et al.* 2008). In addition, the finding of rCBF changes in putamen is in accordance with the motor deficit similar to Parkinson's disease found by Lieberman *et al.* (1995) in alpinists climbing Mount Everest, suggesting that frontal-striatal circuits could have been impaired by high altitude. The sensitivity of motor areas to acute hypoxia speaks in favour of a direct effect of hypobaric hypoxia also on psychomotor activity.

Acute Mountain Sickness has a latency of hours since the acute exposition to critical heights (2500–3500 m a.s.l.) and consequently the short exposition time in the present experiment does not allow conclusive inferences on such crucial matter in high-altitude medicine.

Limitations of the study and methodological aspects

The main limitation of the study was the relatively small number of subjects investigated due to the high costs of the implemented methodology. This resulted in a not very strict statistical threshold increasing the likelihood of Type II statistical errors even though the within-subjects design of the study conferred certain robustness to the results. However, the trend of significance confirmed both the previous investigation and the present working hypothesis.

The analysis performed by Computerized Brain Atlas (CBA) in our previous report was conceptually different from the present one performed by SPM. Even though spatial standardization, intensity normalization and smoothing procedures show several similarities, the two software perform statistical analyses from different points of view. SPM implements univariate analysis creating t-statistic based maps; CBA utilizes the data from VOIs to feed mostly multivariate analyses, enabling to investigate more general statistical effects. The implications of such different approaches are various. CBA cannot analyse regions smaller than the pre-defined VOIs corresponding to the anatomo-functionally defined BAs and often misses fine local changes. Conversely SPM analysis is conducted at cluster of voxel level, being the size threshold chosen according to the spatial resolution of the camera. Hence, SPM in general does not analyse regions defined *a priori* but identifies only local changes clustering in a number of voxels exceeding the determined threshold.

In SPM spatial smoothing performed with a spatially stationary Gaussian filter and kernel widths of up to 16 mm is being used in the literature. The purpose of spatial smoothing is to cope with functional anatomical variability that is not compensated by spatial normalization and to improve the signal to noise ratio. The kernel filter of 10 mm in the present study has been chosen to approach the size of the signal to detect, the system spatial resolution (11 mm for our SPECT camera) (Rosenfeld & Kak 1982).

The choice to restrict the regional analysis to BAs as close as 2 mm to the Talairach transformed SPM output isocenters coordinates has been made to minimize the impact of partial volume effect in order to report as precisely as possible the grey and white matter regions involved in the response to hypobaric hypoxia.

The implementation of voxel-based analysis disclosed regional perfusion differences between acute hypobaric hypoxia and normobaric normoxia mainly in the sensorymotor cortex and prefrontal lobe. These functional neuroimaging findings support the conclusions of several previous investigators reporting neuropsychological impairment in functions pre-dominantly processed in the frontal lobes. The differential physiological sensitivity of various brain regions to hypobaric hypoxia may have relevant neuropathological and clinical implications.

Conflicts of interests

None.

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