



SHORT COMMUNICATION

Brain structure and neurocognitive function in two professional mountaineers during 35 days of severe normobaric hypoxia

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Abstract

Background and purpose: Animal studies suggest that exposure to severe ambient hypoxia for several days may have beneficial long-term effects on neurodegenerative diseases. Because, the acute risks of exposing human beings to prolonged severe hypoxia on brain structure and function are uncertain, we conducted a pilot study in healthy persons.

Methods: We included two professional mountaineers (participants A and B) in a 35-day study comprising an acclimatization period and 14 consecutive days with oxygen concentrations between 8% and 8.8%. They underwent cerebral magnetic resonance imaging at seven time points and a cognitive test battery covering a spectrum of cognitive domains at 27 time points. We analysed blood neuron specific enolase and neurofilament light chain levels before, during, and after hypoxia.

Results: In hypoxia, white matter volumes increased (maximum: A, 4.3% ± 0.9%; B, 4.5% ± 1.9%) whilst gray matter volumes (A, -1.5% ± 0.8%; B, -2.5% ± 0.9%) and cerebrospinal fluid volumes (A, -2.7% ± 2.4%; B, -5.9% ± 8.2%) decreased. Furthermore, the number (A, 11–17; B, 26–126) and volumes (A, 140%; B, 285%) of white matter hyperintensities increased in hypoxia but had returned to baseline after a 3.5-month recovery phase. Diffusion weighted imaging of the white matter indicated cytotoxic edema formation. We did not observe changes in cognitive performance or biochemical brain injury markers.

Sven-Erik Sönksen and Sven Kühn contributed equally.

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Discussion: In highly selected healthy individuals, severe sustained normobaric hypoxia over 2 weeks elicited reversible changes in brain morphology without clinically relevant changes in cognitive function or brain injury markers. The finding may pave the way for future translational studies assessing the therapeutic potential of hypoxia in neurodegenerative diseases.

KEYWORDS

acute mountain sickness, brain recovery, hypoxic limits of the brain, performance, white matter hyperintensities

INTRODUCTION

Excessive neuronal oxidative stress and insufficient oxidative stress resistance characteristically occur in the aging brain. This imbalance probably contributes to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis or amyotrophic lateral sclerosis. Moreover, oxidative stress promotes demyelination, cell cycle arrest and cell death, which may eventually limit neuronal regeneration. The therapeutic potential of hypoxia as a means of controlling oxidative stress has therefore been investigated in human cell and animal studies. In a mouse model of Friedreich's ataxia, breathing 11% O₂ diminished ataxia progression [1]. Concordantly, chronic hypoxia (11% O₂) prevented symptom development in a mouse model of the Leigh syndrome, a mitochondrial disease [2]. Yet, translating these findings from animals to patients could be limited by the adverse effects of severe hypoxia on brain tissue integrity and function. Indeed, graded decompression of healthy individuals to an ambient pressure equivalent to the summit of Mount Everest substantially worsened grammatical reasoning [3], psychomotor performance and mental efficiency [4].

Hypoxic cerebral injury is another concern. Sixteen hours of 12% normobaric hypoxia led to sodium accumulation in the cerebral extracellular space resulting in ionic edema [5]. Furthermore, cerebral magnetic resonance imaging (MRI) studies showed reversible local vasogenic and cytotoxic white matter edema in mountaineers returning from high altitude [6]. Irreversible damage to white and gray matter was seen after returning from extreme altitude [7].

Whether severe normobaric hypoxia, intended for therapeutic purposes, adversely affects cerebral function and integrity in healthy individuals is unknown.

In a pilot study applying normobaric hypoxia corresponding to approximately 7000 m altitude for several weeks [8], whether chronic severe hypoxia produces clinical findings in cerebral MRI, changes in blood brain injury biomarkers and a decline in neurocognitive function was assessed in two healthy individuals.

MATERIALS AND METHODS

At the German Aerospace Center, two healthy professional mountaineers were enrolled in a 35-day normobaric hypoxia study. Participant A (male, 57 years) had extensive experience with

>8000-m altitude and participant B (female, 49 years) with altitudes up to 6000 m. During the study, arterial partial pressures of oxygen decreased to a minimum of 36 mmHg in participant A and 33 mmHg in participant B [8]. The protocol was approved by the North Rhine Medical Association ethics committee and conducted according to the Declaration of Helsinki (pre-registration DRKS00013772) after written informed consent was obtained.

Cerebral MRI (3-T Siemens Biograph), with morphological sequences, susceptibility weighted imaging (SWI), arterial angiography and diffusion tensor imaging (DTI), was obtained 1 month before, once during acclimatization, three times in hypoxia, and after 1 and 4 months of recovery. During transfer to and examinations in the MRI facility, hypoxia was maintained by breathing equivalent hypoxic gas mixtures through a face mask from a Douglas bag. Based on T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) imaging, cerebrospinal fluid and white and gray matter volumes were acquired [9]. The open source FreeSurfer image analysis suite was applied (v7.1.0; <http://surfer.nmr.mgh.harvard.edu/>). Images were automatically processed with the longitudinal stream in FreeSurfer to extract reliable volume estimates (Appendix S1). White matter hyperintensities were quantified from preprocessed fluid attenuated inversion recovery (FLAIR) images. Subsequently, hyperintensities were assigned to atlas-based brain regions [10]. DTI acquisitions were processed using the ENIGMA-DTI pipeline (<http://enigma.ini.usc.edu>), based on the FSL package TBSS [11], to measure average whole-brain fractional anisotropy value and average tract fractional anisotropy values for predefined white matter tracts. Additionally, axial and radial diffusivity and mean diffusivity were measured. Built-in 3D slicer modules were applied to determine basilar skull artery volumes from high-resolution 3D time-of-flight angiography and superior sagittal sinus volumes from an isotropic high-resolution T2-weighted sequence. Morphological sequences as well as SWI were evaluated by two blinded radiologists (Appendix S1).

Cognitive performance was tested 28 out of 35 study days with the cognition test battery developed for NASA and designed for astronauts. Cognition comprises 10 brief tests covering various cognitive domains (Appendix S1) [12]. Data were corrected for practice and stimulus set difficulty effects prior to analysis [13].

The brain injury markers neurofilament light chain and neuron specific enolase were determined in blood samples collected on study days 0, 16, 21, 27, 32 and 35 and after 30 days of recovery.

RESULTS

Both participants experienced high-altitude-like sickness without progression to relevant cerebral edema.

Compared with baseline, white matter volumes increased in hypoxia up to 4.3% in A and 4.5% in B (95% confidence interval A, 3.4, 5.1; B, 2.6, 6.4). Gray matter volumes did not show consistent changes. Cerebrospinal fluid volumes decreased by 2.7% in A and by 5.9% in B during hypoxia (95% confidence interval A -5.1, -0.3; B, -12.1, 2.3). Whereas in both, intracranial arterial volumes increased in hypoxia (maximum: A, +8.1%; B, +5.1%), intracranial venous volumes responded differently with a steady increase until the end of hypoxia in A and a steady decrease in B.

The number and volume of white matter hyperintensities increased in hypoxia but rapidly resolved during recovery (Figure 1). Averaged white matter diffusion values indicated an emerging cytotoxic edema component with a maximum during the second hypoxia measurement and partial regression early into the recovery phase. Microhemorrhages were not detected.

Under hypoxia, cognitive speed was significantly faster for three tests (digit symbol substitution, line orientation and visual object learning), whilst it was significantly slower for the balloon analog risk test only (Figure 1). Across all domains, speed was significantly faster (+0.28 SD, $p = 0.028$) whilst cognitive accuracy exhibited no significant changes (+0.04 SD, $p = 0.71$) under hypoxia. Standardized risk-taking propensity on the balloon analog risk task was 0.47 standard deviations higher in the low compared to the high oxygen condition (+0.27 SD; $p = 0.0921$).

Hypoxia-associated biochemical signal of brain damage was not detected. Neuron specific enolase, a neuronal damage marker, remained low in both participants in hypoxia (A, normoxia $23.5 \pm 12.0 \mu\text{g/l}$, hypoxia $22.7 \pm 3.5 \mu\text{g/l}$; B, normoxia $15.4 \pm 1.1 \mu\text{g/l}$, hypoxia $18.2 \pm 3.0 \mu\text{g/l}$). No obvious reasons were found for the slight, intermittent, neuron specific enolase increase up to $37.3 \mu\text{g/l}$ in subject A during reoxygenation. Concordantly, neurofilament light chain, a marker for axonal damage, did not increase in hypoxia in either participant (A, normoxia $14.6 \pm 0.8 \text{ pg/ml}$, hypoxia $13.9 \pm 1.3 \text{ pg/ml}$; B, normoxia $8.6 \pm 0.7 \text{ pg/ml}$, hypoxia $7.2 \pm 0.9 \text{ pg/ml}$).

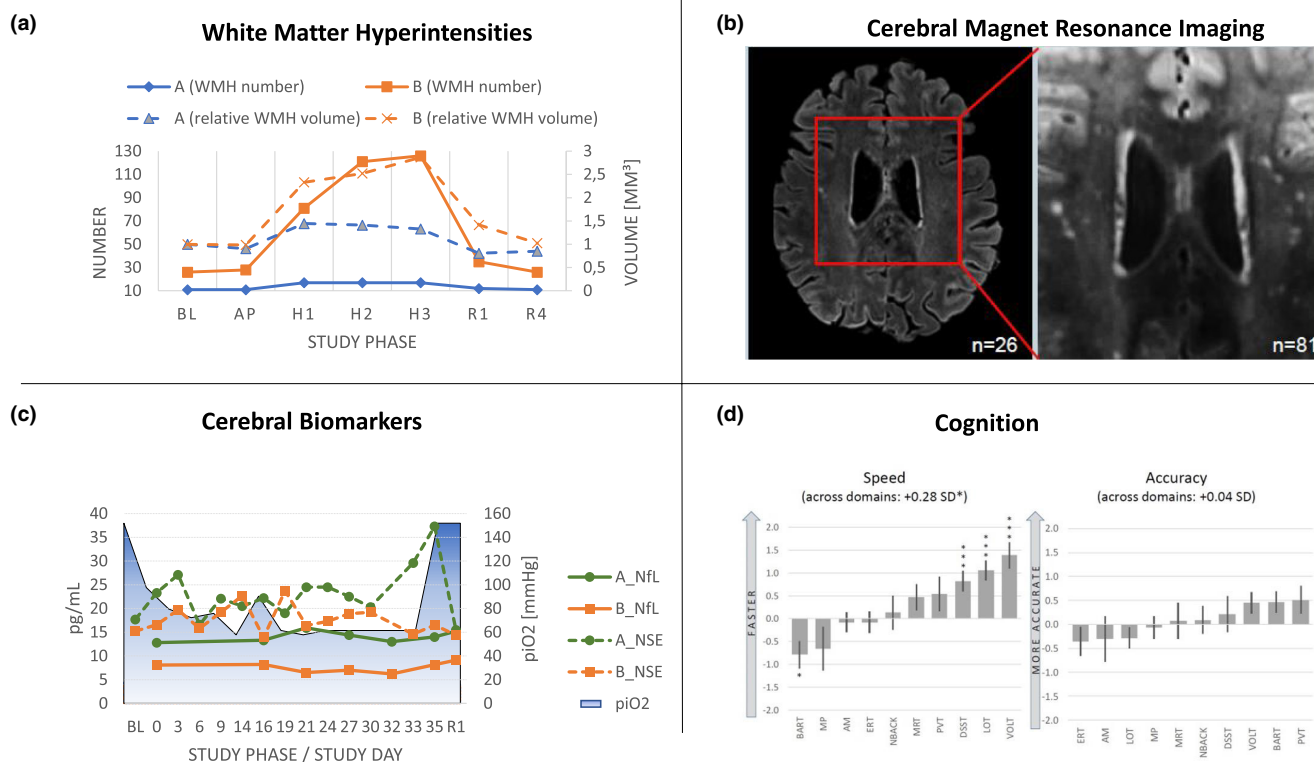


FIGURE 1 Results of cerebral magnetic resonance imaging, neurocognitive function testing and biochemical markers of brain injury. (a) Number and volume of white matter hyperintensities over the course of the study (participant A, blue; participant B, orange): BL, baseline; AP, acclimatization; H1–H3, hypoxia; R + 1, recovery after 1 month; R + 4, recovery after 4 months. (b) Representative MRI (T2-FLAIR transversal) sequences showing white matter hyperintensities which emerged in hypoxia. (c) Normobaric hypoxia effects on biochemical markers (participant A, blue; participant B, orange; inspiratory oxygen level, blue area): BL, baseline; AP, acclimatization; H1–H3, hypoxia; R + 1, recovery after 1 month. (d) Normobaric hypoxia effects on cognitive performance shown as the average for both individuals: BART, balloon analog risk test; MP, motor praxis task; AM, abstract matching; ERT, emotion recognition task; NBACK, working memory test; MRT, matrix reasoning test; PVT, psychomotor vigilance test; DSST, digit symbol substitution task; LOT, line orientation test; VOLT, visual object learning test [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

DISCUSSION

Several weeks of sustained severe normobaric hypoxia did not lead to irreversible structural or functional brain changes. Strikingly, MRI findings in hypoxia, like white matter hyperintensities, were disconnected from cognitive function and from relevant changes in biomarkers of neuronal (neuron specific enolase) and axonal damage (neurofilament light chain). Yet, volume changes of intracranial compartments during hypoxia were observed, suggesting maladaptation on the tissue level.

Because hypoxic cerebral vasodilation contributes to cerebral edema formation [14], the large increase in white matter hyperintensity number and volume in our female participant was interpreted as local vasogenic edema formation, probably caused by capillary barrier breakdown. It is speculated that her higher white matter hyperintensity burden at baseline may result from lower white matter integrity, which in turn could increase the susceptibility to hypoxia. However, a gender effect seemed unlikely because a similar phenomenon was also discovered in a male individual after 1 week at 4559 m [6]. White matter seems particularly susceptible for hypoxic stress, which causes an increased serum filament level, a marker for neuro-axial injury, in healthy participants 44 h after ascending actively to 4454 m [15]. After 3 months of recovery, cerebrovascular alterations had regressed completely in our participants, which is in good agreement with the transient nature of hypobaric hypoxia induced cerebral responses [6].

Our findings confirm that the acclimatized human brain exhibits remarkable hypoxia tolerance. Accuracy of cognitive function was unchanged whilst speed increased slightly but significantly across the domains digit symbol substitution, line orientation and visual object learning performance. The latter can probably be attributed to continued small practice effects beyond the fifteenth repetition of the cognition test [13]. The balloon analog risk test was the only test that exhibited significant slowing and simultaneous non-significant increases in risk taking. Incidentally, impaired grammatical reasoning and an increased number of transposed digits during everyday conversations was also recognized in both participants. Overall our findings suggest that the two experienced mountaineers were able to maintain cognitive function in the face of substantial hypoxia.

Our participants were professional mountaineers and are therefore not representative for the average population. Additional studies in patients with neurodegenerative disease are required. Initially, such studies should be limited to hypoxia experienced patients, which appears feasible considering that several mountaineers with neurodegenerative diseases have summited Mount Everest.

Our results suggest that severe sustained normobaric hypoxia is tolerated in highly selected individuals and may pave the way for future translational studies of the therapeutic potential of hypoxia in neurodegenerative diseases [1].

AUTHOR CONTRIBUTIONS

Sven-Erik Soenksen: Formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal). **Sven Kuehn:** Formal analysis (equal); investigation (equal); writing – review and editing (equal). **Mathias Basner:** Formal analysis (equal);

investigation (equal); methodology (equal); writing – review and editing (equal). **Darius Gerlach:** Formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Fabian Hoffmann:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Christian Muehl:** Formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Jens Tank:** Conceptualization (equal); investigation (equal); project administration (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Hans-Juergen Noblè:** Formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Katja Akguen:** Conceptualization (supporting); resources (supporting); writing – review and editing (equal). **Tjalf Ziemssen:** Conceptualization (equal); investigation (equal); resources (equal); writing – review and editing (equal). **Jens Jordan:** Conceptualization (equal); funding acquisition (equal); supervision (equal); writing – review and editing (equal). **Ulrich Limper:** Conceptualization (lead); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

This study was supported by the programmatic funding of the German Aerospace Center (DLR). Dr Sven-Erik Sönksen has nothing to disclose related to this project. Dr Sven Kühn has nothing to disclose related to this project. Professor Mathias Basner has nothing to disclose related to this project. Dr Christian Mühl has nothing to disclose related to this project. Dr Darius Gerlach has nothing to disclose related to this project. Dr Fabian Hoffmann received funding from the German Aerospace Center (DLR, 50WB1517) and the Bundesministerium fuer Bildung und Forschung (BMBF, 50WB1816). Professor Jens Tank has nothing to disclose related to this project. Dr Hans-Juergen Noblè has nothing to disclose related to this project. Professor Katja Akgün has nothing to disclose related to this project. Professor Tjalf Ziemssen has nothing to disclose related to this project. Professor Jens Jordan has nothing to disclose related to this project. Dr Ulrich Limper received funding from the internal grant program (project IFF 2020-26) of the Faculty of Health at Witten/Herdecke University, Germany, and from the German Aerospace Center (DLR, 50WB2119) during the conduct of this study.

DATA AVAILABILITY STATEMENT

The authors declare that anonymized data will be shared from the corresponding author upon reasonable request from any qualified investigator.

TRANSPARENCY DECLARATION

The lead author affirms that this paper is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

TRIAL REGISTRATION

The study was pre-registered on 16 January 2018 on the German Clinical Trial Registry (DRKS) under ID DRKS00013772.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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