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Acute hypoxic gas breathing severely impairs cognition and task learning in humans

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HIGHLIGHTS

- We induced hypoxia in healthy adults with a hypoxic gas mixture and sham treatment.
- We measured neurocognitive processes that were vulnerable to oxygen deprivation.
- Hypoxia caused a range of severe cognitive deficits and impaired task learning.
- The frontal cortex and hippocampus appear particularly vulnerable to hypoxia.
- Similar impairments are seen in high altitude exposure & mild traumatic brain injury.

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ABSTRACT

Impairments in neural function are common when oxygen supply to the brain is reduced. This study examined neurocognitive processes that are vulnerable to oxygen deprivation. We induced moderate-to-severe hypoxia in healthy adults, thereby inducing impairments caused by low brain oxygen availability. 22 healthy adults participated in this matched-pairs study with a single-blind, randomised design. Baseline neurocognitive function was examined during a familiarisation trial and participants were assigned to hypoxia (10% O_2) or sham (21% O_2) groups. Neurocognitive performance was assessed via computerised test battery after 50 min of breathing a gas mixture that reduced arterial oxygen saturation by 20% ($p < 0.01$). Hypoxia severely reduced performance across all neurocognitive domain scores; with significant drops in neurocognitive index (−20%), composite memory (−30%), verbal memory (−34%), visual memory (−23%), processing speed (−36%), executive function (−20%), psychomotor speed (−24%), reaction time (−10%), complex attention (−19%) and cognitive flexibility (−18%; all $p < 0.05$). Practice effects were blocked by hypoxia but occurred in sham for information processing speed (+30%), executive function (+14%), psychomotor speed (+18%), reaction time (+5%), cognitive flexibility (+14%), and overall cognitive functioning (+9%; all $p < 0.05$). Neuropsychological performance decrements caused by acute experimental hypoxia are comparable to cognitive domains impaired with high altitude exposure and mild traumatic brain injury.

1. Introduction

The brain requires an uninterrupted supply of energy in order to function effectively. Neurons have only a minimal capacity to store energy and as such rely upon a constant supply of oxygen to support the high and fluctuating energy demands required to support complex processing. These factors render the cells within the central nervous system (CNS) highly susceptible to dysfunction and damage during even relatively short bouts of anoxia and ischemia.

Basic cognitive dysfunction has been observed during residence at high altitude, where inspired oxygen pressure is reduced. Various experimental models of acute hypoxia can be used to simulate neurological deficits caused by the lowered oxygen availability experienced with residence at altitude and during aviation emergencies [7,13,47]. Such impairments are dependent on the level of altitude simulated. It has been acknowledged that exposure to altitudes as low as 2000 m can cause negative symptoms of hypoxia that are thought to be related to a cerebral effect [22]. Similarly, compressed gas mixtures and rebreathing equipment used in technical and commercial diving can fail or be incorrectly operated causing similar hypoxic emergencies. A fuller understanding of psychological outcomes associated with hypoxia may help inform strategies for managing exposure to extreme environments or equipment malfunctions.

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As the metabolic demand of neuronal tissue increases by 15% during tasks that require cognitive and other neurological functions [15,19,39,45], neural dysfunction caused by dysfunctional or compromised aerobic metabolism manifests as functional disability — the extent of which tends to indicate the severity of the hypoxia. Prolonged exposure to hypoxia ultimately leads to an inability to maintain neuronal integrity and irreparable brain injury. Cognitive impairments are common among survivors of severe forms of hypoxic–ischemic brain injury whereby prolonged periods of hypoxia result in brain tissue death and symptoms that persist beyond the duration of the initial injury [2,4,23,24,36,37,48,49]. Decrements in higher-level cognitive functions most frequently documented in these studies include disturbances to processing speed, memory and executive function. Such impairments are also prevalent in mild forms of hypoxic–ischemic brain injury, such as mild traumatic brain injury, and can persist for prolonged periods after the initial injury [3,17]. A better understanding of the profile of neuropsychological deficits that develop during hypoxia may provide novel insight into neural process that are vulnerable to global oxygen deprivation and are impaired during the initial stages of hypoxic–anoxic brain injuries.

In this study we use a hypoxia intervention to experimentally induce global oxygen deprivation similar to the metabolic crisis that occurs during sudden exposure to reduced oxygen availability. We investigated the effects of compromised oxygen delivery across a range of neurocognitive domains and perceptual experiences. We hypothesised that acute moderate–severe hypoxia would compromise functions predominately involving prefrontal neural regions and the hippocampus, predicting that the trends in dysfunction during exposure to the hypoxia intervention will be similar to those that develop and persist when oxygen delivery to the brain is compromised by hypoxic–ischemic injury.

2. Materials and methods

2.1. Participants and experimental design

Twenty-two healthy adult participants (10 males, 12 females) with a mean age of 23 years (20–28 years) volunteered to participate. Participants were recruited via a tertiary education institution. All participants gave written informed consent and were screened for health complications related to the *Oxygen Manipulation*. The study was conducted with accordance to the declaration of Helsinki and approved by the institutional ethics committee. Participants were eligible to participate in the study if they were between the ages of 18 to 60 years old and had no known neurological, cardiovascular or mental health issues. Participants were assigned to an oxygen manipulation group (hypoxia or sham) in a pseudorandom order to ensure minimal variance pairing by age, gender and anthropometric variables (height and mass). Retrospective evaluation of matched pairs on baseline neurocognitive index score was also assessed (see Table 1).

2.2. Measures

2.2.1. Neuropsychological assessment

A standardised, brief (approximately 30 min) and automated computerised battery of neuropsychological tests was used to assess neuropsychological function (CNS Vital Signs; http://www.cnsvs.com/; [21]). The test battery comprised seven tests: verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention and a continuous performance test. A detailed description of each test is given by Gualtieri and Johnson [21]. All tests were initiated and supervised by one experimenter and delivered unassisted and uninterrupted using a single computer to ensure consistency in administration. Scoring is automated, eliminating variability and rater bias. Raw test scores, domain scores compared to age-adjusted norms, and an overall neurocognitive index are calculated. It is designed for serial administration and is suitable for baseline and follow-up assessments. Its large normative sample ($n = 552$) includes those aged 8 to 89. Standardised computer instructions on how to complete each test were given prior to the test along with practice sessions where required.

Test scoring in the CNS Vital Signs battery is generated from 17 primary scores based on correct responses, error responses, number of responses and reaction times. Primary scores are used to generate nine neurocognitive domain scores that reflect basic mental functions: Composite memory, verbal memory, visual memory, processing speed, executive function, psychomotor speed, reaction time, complex attention and cognitive flexibility and an overall neurocognitive index score. Domain scores are generated as raw scores and then computed as standard scores, which represent the participants' raw score relative to a proprietary age-matched normative data set of healthy individuals.

Standardised domain scores and the 17 primary scores were calculated relative to each participant's baseline score collected in the first experimental session and used for statistical analyses.

2.2.2. Assessment of perceptual experiences

An adaptation of the Environmental Symptoms Questionnaire [28] using selected measures deemed most relevant to the current experiment was used to assess a range of perceived experiences relating to

Table 1
Participant characteristics.
Descriptive statistics for pairs allocated to hypoxia and sham oxygen manipulation groups. Comparisons between groups are independent samples t-tests. NCI; neurocognitive index (aged-matched percentile score).

Hypoxia						Sham					
#	Gender	Age (years)	Mass (kg)	Height (cm)	Baseline NCI (%)	#	Gender	Age (years)	Mass (kg)	Height (cm)	Baseline NCI (%)
1	F	23	68	168	58	1	F	20	60	160	34
2	F	22	59	162	97	2	F	25	61	165	34
3	F	22	105	175	40	3	F	24	83	174	58
4	F	21	60	168	91	4	F	23	54	165	57
5	F	21	61	163	68	5	F	22	60	164	73
6	F	28	64	162	88	6	F	23	58	168	84
7	M	26	91	183	73	7	M	21	76	171	73
8	M	24	89	188	88	8	M	26	82	183	82
9	M	22	78	167	66	9	M	21	92	184	42
10	M	26	78	185	37	10	M	24	80	183	27
11	M	24	102	180	58	11	M	25	99	188	61
Mean		23	78	173	70	Mean		23	73	173	57
SD		2	17	10	20	SD		2	15	10	20
t Statistic		0.5	0.7	−0.1	−1.5						
p Value		0.6	0.5	0.9	0.2						