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Research

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The effects of mild, acute hypoxia on cognitive performance

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SSM perspective

Background

The Swedish nuclear power plant Forsmarks Kraftgrupp AB (FKA) reported that they wanted to use a fire prevention method by reducing the oxygen level down to 15% in some locations. The personnel is only going to work there for a limited number of hours. This fire protection method has never been used before in any nuclear power plant in spaces where people work.

The background to the study was the lack of comparable, sufficiently relevant scientific literature on the topic of whether cognitive ability deteriorates or not when the oxygen (O2) level is reduced from the normal level (21%) to 15%, without habituation. SSM needed more knowledge of whether the cognitive abilities of the personnel could be affected in a negative way. The goal of the study was to provide SSM with the basis for oversight.

Objectives

The study was divided into two parts, a literature study and an experimental part. The phenomenon studied was comparable to the situation at the nuclear power plant. The persons involved in the experimental phase were exposed to a change from normal oxygen level to a reduced oxygen level without having time to adapt. The exposure to 15% oxygen was 2 h during the first exposure, 2 h during the second exposure and 45 min during the third and final exposure.

Results

The literature review primarily identified evidence that the effects on cognitive performance due to hypoxia at 15% O2, if any, would be small. A few researchers have reported findings that support adverse effects on cognitive performance already at 16-15% O2 concentration. In support of the hypothesis that no adverse effects on cognitive performance could be observed under conditions studied, there were no significant decreases in cognitive performance as a result of exposure to the experimental conditions with 15% O2.

This study was clearly delineated and several possible influencing aspects were not included. Therefore, we cannot rule out possible interaction effects, with negative impact on cognitive ability, between hypoxia and other factors such as diseases, medication and drugs, concussion history, or other aspects of air quality.

Need for further research

There are several aspects of this research that should be of interest for further research by the nuclear industry. SSM has no plans to fund further research.

Project information

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Content

Figures

Tables

1. Executive Summary

Room air with reduced oxygen (O_2) levels that prevent materials to ignite and combust is a cost-effective and increasingly popular fire prevention method. For system safety reasons, the effects of hypoxia, i.e. the lack of sufficient O_2 (i.e. less than 21% O_2 which is the approximate oxygen level of normal room air), on cognitive performance of persons working under such conditions are important to investigate. This report presents a study commissioned by the Swedish Radiation Safety Authority (Strålsäkerhetsmyndigheten, SSM) with GEISTT AB[1] as provider of the research. The rationale was to investigate system safety concerns of staff working in confined spaces with 15% O_2 as a fire prevention method at the Swedish nuclear power plant of Forsmark Kraftgrupp AB (FKA). The study was conducted in two steps, starting with an extensive literature review followed by an experiment. These are both presented in this report.

The review of the scientific literature focused on cognitive effects of mild normobaric hypoxia. The review exhibits inconclusive evidence, although existing findings imply that cognitive performance deficiencies induced by mild, acute hypoxia can be expected to be minor, if present at all. The earliest cognitive signs and symptoms of hypoxia are typically experienced around 16-15% O_2, and can be observed in visual perception. There are a few studies that have found indications of other minor cognitive effects at rather mild stages of hypoxia, but results from the different studies are inconclusive, partly due to that a wide range of conditions and measures have been studied and partly since a relatively low number of experimental studies specifically have studied cognitive effects of mild, acute hypoxia under normobaric conditions. Section 4.3.6 presents the conclusions from the literature review.

Following the literature review, an experiment on the effects of mild, acute hypoxia on cognitive performance was conducted with 18 participants. They were exposed to conditions matching that of nuclear power plants service staff, who work a maximum of three 2 hour sessions per day in 15% O_2 with breaks of 15 after the first session and 30 minutes after the second session. Cognitive performance was measured using the commercially available cognitive tests King-Devick and Automated Neuropsychological Assessment Metrics. All measurements during training, baseline, experimental conditions, and post-testing, were conducted during seated rest. No cognitive decrements due to the mild, acute hypoxia were detected (see Section 7.1 for empirical conclusions of the study).

To summarize, the literature review identified inconclusive evidence that effects on cognitive performance due to hypoxia at 15% O_2, if any, would be minor. However a few researchers has reported findings supporting that negative effects on cognitive performance may appear already when the O_2 level is reduced down to 16-15%. In support of the null hypothesis, the experiment showed no significant decrements on cognitive performance as an effect of the exposure to the experimental condition of 15% O_2. It is concluded that the null hypothesis stating that there are no effects on cognitive performance on this O_2 level should be retained, and that any noticeable negative effects of mild, acute hypoxia on cognitive performance would plausibly appear be induced by interaction effects between hypoxia and other factors, such as diseases, medication and drugs, concussion history, or other aspects of air quality.

[1] GEISTT AB – Group for Effectiveness, Interaction, Simulation, Technology, and Training – is a Sweden-based company offering human-centered consultancy services, methods & tools, and provision of applied research & development projects. For more information, please visit www.geistt.com.

2. Sammanfattning

En kostnadseffektiv och alltmer populär metod för brandskydd är användningen av rumsluft med minskad koncentration syre (O_2) för att hindra materials benägenhet att antändas och förbrännas. Av system-säkerhetsskäl så är effekterna av hypoxi, dvs. en O_2-koncentration lägre än de 21% O_2 som är den ungefärliga syrenivån normal rumsluft, på kognitiv prestation för personer som arbetar under sådana förhållanden viktiga att undersöka. Denna rapport presenterar forskning som utförts av GEISTT AB på uppdrag av Strålsäkerhetsmyndigheten (SSM). Syftet var att undersöka system-säkerhetsfrågor gällande kognitiv förmåga hos personal som arbetar i utrymmen med 15% O_2 som en brandförebyggande metod vid det svenska kärnkraftverket i Forsmark Kraftgrupp AB (FKA). Studien genomfördes i två steg, som började med en omfattande litteraturgenomgång följt av ett experiment. Resultaten från båda dessa steg presenteras i denna rapport.

Genomgången av den vetenskapliga litteraturen fokuserade på de kognitiva effekterna av mild, normobar hypoxi (dvs. syrebrist under normalt atmosfärstryck). Granskningen visar inte helt entydiga bevis, även om befintlig forskning i huvudsak visar att effekter av mild, akut hypoxi har mycket liten, om någon, påverkan på kognitiv förmåga. De tidigaste kognitiva tecknen och symtom på syrebrist har observerats kring 16-15% O_2, och gäller visuell perception under mörkerförhållanden. Det finns några studier som har funnit indikationer på andra mindre kognitiva effekter vid tämligen milda stadier av hypoxi, men resultaten från de olika studierna är ofullständiga, delvis på grund av att ett stort antal förutsättningar och variabler har studerats, och dels eftersom ett relativt lågt antal experimentella studier specifikt studerat kognitiva effekter av mild, akut hypoxi under normobara förhållanden. I Avsnitt 4.3.6 presenteras slutsatserna från litteraturgenomgången.

Utifrån litteraturgenomgången planerades och genomfördes ett experiment avseende effekterna av mild, akut hypoxi på kognitiv förmåga med 18 deltagare. Deltagarna exponerades för hypoxiska förhållanden motsvarande dem som FKA servicepersonal arbetar under. Detta innebär högst tre 2 timmars arbetspass per dag i 15% O_2, med rast i normal luft på 15 min efter första arbetspasset och 30 min efter andra arbetspasset. Kognitiv förmåga mättes med hjälp av de kommersiellt tillgängliga kognitiva testverktygen King-Devick samt Automated Neuropsychological Assessment Metrics. Alla mätningar under träning, baslinjetestning, testning under experimentella förhållanden, samt efter-test genomfördes under sittande vila. Inga kognitiva försämringar till följd av mild, akut hypoxi observerades (se Avsnitt 7.1 för slutsatser från studien).

Sammanfattningsvis, under litteraturgenomgången identifierades främst bevis för att effekterna på kognitiv förmåga på grund av syrebrist vid 15% O_2 kunde förväntas vara små, om ens förekommande. Enstaka forskare har dock rapporterat fynd som stödjer att negativa effekter på kognitiv förmåga kan observeras redan vid 16-15% O_2-koncentration. Till stöd för nollhypotesen, dvs. att inga negativa effekter på kognitiv förmåga skulle observeras under studerade förhållanden, så observerades inga signifikanta minskningar på kognitiv förmåga som en effekt av exponeringen för den experimentella betingelsen med 15% O_2. Slutsatsen är att nollhypotesen behålls, dvs. inga negativa effekter på kognitiv förmåga vid 15% O_2 är att förvänta. Det påpekas dock att interaktionseffekter mellan hypoxi vid 15% O_2 och andra faktorer, såsom sjukdomar, medicinering och droger, hjärnskakning historia, eller andra aspekter av luftkvaliteten, skulle kunna ge en negativ påverkan på kognitiv förmåga.

3. Author Note

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4. Introduction

The reported studies were commissioned by the Swedish Radiation Safety Authority (Strålsäkerhetsmyndigheten, SSM) to inform them on cognitive effects of mild, acute hypoxia, under normobaric conditions (i.e. ground level atmospheric pressure). The background for SSM's interest is that one Swedish nuclear power plant, run by Forsmarks Kraftgrupp AB (FKA), has received an exempt from the Swedish Work Environment Authority regulations (§ 6 of AFS 1997:07 concerning gases regarding supplemental oxygen when the oxygen level is below 18%), to reduce oxygen (O_2) levels to 15% (allowed to vary from 14.5-15.5%) (Swedish Work Environment Authority, 2011) in certain work spaces, or fire cells, to drastically reduce the risk of fire.

While there is extensive knowledge of physiological and cognitive effects of more severe hypoxia under hypobaric and hyperbaric conditions, the specific knowledge of cognitive effects of mild, normobaric hypoxia is inconclusive. The majority of studies available in the scientific literature report on work conducted under hypobaric (i.e. below atmospheric pressure) or hyperbaric (i.e. above atmospheric pressure) conditions, from domains such as mountaineering, aviation, and diving. Hypoxia under such conditions has been studied for many decades and well-established guidelines and handbooks are available, for example the US Air Force Aerospace and Operational Physiology Handbook (Woodrow & Webb, 2011).

Hypoxic air under normobaric conditions (i.e. reduced oxygen levels under normal atmospheric pressure) in normal work settings has gained popularity during the last two decades and is for example used for fire prevention and fire extinction, to preserve cultural heritage in museums and archives, for conservation of food, and for altitude/hypoxia training. As a result, the number of employees with "normal" jobs that are exposed to hypoxic conditions in their professional work setting is increasing. On a side note, it should also be mentioned that many jobs may expose employees to hypoxic conditions even though not intentionally induced for fire protection or other purposes. For jobs where hypoxic conditions are (e.g. reduced O_2 for fire prevention or conservation) or may be present (e.g. control/maintenance inside large cisterns), personal oxygen sensors with automatic warnings should be used at all times.

Based on a review, Jensen & Nygaard (2013) has presented a "threshold value" at a minimum of 17% O_2 concentration at which the human body does not display any adverse effects (17% O_2 is equivalent to the air at 1,500 m/5,000 ft above sea level while normal room air contains approx. 21% O_2). Hypoxic air systems used for fire prevention typically maintain an O_2 level of 15%. This corresponds to the oxygen level at an altitude of 2,700 metres (9,000 ft) above sea level, and is approximately the same oxygen conditions as in the cabin of a commercial airliner. In a study by Hampson, Kregenow, Mahoney, Kirtland, Horan, et al. (2013) 10% of the 207 observed flights reached an oxygen level of 15.5% O_2, equivalent to 2,400 m. According to Jensen & Nygaard, the risks for healthy persons remaining in an environment with 15% O_2 for several hours are considered minimal. Angerer & Novak (2003) describes that a lowered oxygen level in the range of 13-15% O_2 prevents most materials from being ignited by fire. This is due to a changed mixing ratio of oxygen and nitrogen, leading to fewer oxygen molecules available for the combustion process.

4.1. Structure of the report

The reported study consisted of two interrelated parts which are both included here. Initially a literature review of the cognitive effects of mild hypoxia was conducted, which formed the base for the hypothesis that was later experimentally tested. The structure of the report follows the recommendations from the American Psychological Association (APA) in their 6th edition of Publication Manual (American Psychological Association, 2010) concerning headings and content of a report presenting experimental psychological research.

The report starts with a presentation of definitions and explanations on relevant terms of importance to give the reader a basic understanding of the concept of hypoxia prior to reading the more detailed sections that follow. The report continues with an overview of the physiological and cognitive effects imposed on people exposed to hypoxic conditions, ranging from mild to moderate and severe stages. The main section of the literature review continues by presenting a large number of studies with specific relevance to cognitive effects of mild, acute hypoxia under normobaric conditions, followed by several important subsections that are considered to bear relevance for requirements on the utilization of reduced oxygen levels as a fire prevention method in work environments.

The report moves on to describe the hypothesis, method, and results from the experimental phase of the study, and ends with a discussion of conclusions, based on the literature review and the experimental results.

The attached appendices present several matrices of the reviewed publications, and map their relevance to different dimensions of particular interest to the study of hypoxia.

4.2. Rationale for study

Concurrent Swedish research concerning health effects (Eiken, Gennser, Zuber, Linder, & Bergöö, 2011) and cognitive effects (Stöllman, Höljö, Lampa, & Wålinder, 2013) of mild hypoxia has provided important information to SSM and the Swedish Work Environment Authority regarding the decision to grant an exempt to FKA for using reduced oxygen as a fire prevention method. SSM has however decided further investigate a number of related system safety issues. This report describes one of these, focusing on the cognitive effects of mild, acute hypoxia under normobaric conditions.

To preserve independence, the two efforts cited above (Eiken et al., 2011; Stöllman et al., 2013) were not included in the preparation and conduction of the present study. For the present study SSM commissioned an extended literature review and an experiment with no connection to, or interaction with, these concurrent studies or FKA. The results and conclusions from the present study thus provide independent information and knowledge on the effects of mild, acute hypoxia on cognitive performance.

During the exempt period, selected staff members at the nuclear power plant of FKA routinely enters an area with oxygen levels reduced to 15% to conduct inspections, instrument calibrations, and minor maintenance work. The space is a closed system over three floors and with a total are of 19,000 square meters. The exempt allows the staff to work in the hypoxic area for a maximum of three two-hour sessions per day, with two breaks of at least 15 and 30 minutes between sessions one and two, and two and three, respectively. When more physically demanding work is to undertaken, the oxygen level is temporarily increased to normal levels (i.e. 21% O_2) to avoid the risks associated with physical and cognitive reactions due to physical activity under hypoxic conditions.

To compare and contrast the exposure schedule at FKA, several recommendations from other domains have been identified. Küpper, Milledge, Hillebrandt, Kubalova, Hefti, Basnayt et al. (2009), have analysed and provided recommendations concerning health effects of working under hypoxic conditions. They conclude that for a normal work day it is not necessary to include additional pauses if the real or equivalent altitude does not exceed 2,700 m (8,858 ft, 15.5% O_2), since there are no risk for altitude-related disorders. The recommendation from Küpper et al., is that if possible, assuming the work includes full days in hypoxic rooms, persons are advised to leave the hypoxic area for a lunch break. If non-acclimatized persons are exposed to 13-15% O_2 levels, the advice by Küpper et al. is to take a break in normal air for at least 15 min after every 2 hr of exposure. If people are exposed to oxygen levels of 13%, the break should be extended to 30 min. Küpper et al. recommend that non-acclimatized persons should avoid exposure to oxygen levels lower than 12%. People working under hypoxic conditions are advised to leave the hypoxic area if they do not feel well. To return to an area with normal conditions as soon as possible is the single most important recommendation for recovery. Symptoms of hypoxia under the conditions used in rooms with hypoxic air do not appear suddenly, and persons who follow these guidelines will have plenty of time to react to and immediately eliminate symptoms of hypoxia. However, symptoms can be hard to detect due to the insidious nature of hypoxia. If the symptoms disappear completely after 15-30 min, the person can re-enter, if necessary. If someone does not recover within 30 minutes he or she should consult with a specialist in altitude medicine prior to the next exposure.

Paul & Grey's (2002) recommendation, following a literature study of aviation cabin pressure equivalent to altitudes from 8,000 to 10,000 ft (2,438-3,048 m, 15.4–14.2% O_2), is that exposure should be limited to four hours, and if operational requirements dictate longer exposure, supplementary oxygen should be provided.

US Army regulations such as the AR 95-1 (Department of the Army, 2014) requires aircrew to use 100% oxygen, if operating: A) flights at or above 10,000 ft (3,048 m, 14.2% O_2) during flights longer than one hr, B) flights above 12,000 ft (3,658 m, 13.2% O_2) for longer durations than 30 min, and C) flights above 14,000 ft (4,267 m, 12.2% O_2) for any period of time.

To summarize the rationale for this study, the knowledge and research on cognitive effects of mild, acute hypoxia in general, and under normobaric conditions in particular, reported in the scientific literature is inconclusive. This is partly due to that a wide range of conditions and measures have been studied and partly since a relatively low number of experimental studies specifically have studied cognitive effects of mild, acute hypoxia under normobaric conditions.

4.2.1. Caveats and delimitations

- The experiment should aim to test the maximum exposure schedule used at FKA, i.e. three 2 hour sessions during a day with 15 and 30 min breaks between session one and two, and two and three, respectively. It was explicitly commissioned by SSM that the experiment should be designed to address the exposure schedule used at FKA and under the same oxygen level (i.e. 15%). This is important to mention since it is quite common when establishing and/or testing thresholds that more demanding conditions than the expected are studied to establish a safety buffer with some marginal for variations.

- Availability of information concerning the target population, i.e. nuclear power plants service staff, and their real work tasks was very limited. Contact with the target population was intentionally avoided in order to preserve the independence of the study. Results and conclusions from concurrent Swedish research concerning cognitive effects of hypoxia (Stöllman et al., 2013) were not available during planning and execution of the literature study and experimental design, and intentionally not included during later stages of the study due to the independency reasons mentioned above.
- The tests that the participants were exposed to during the experiment are to be considered as cognitive tests of a laboratory nature without explicit linkage to the real work tasks of nuclear power plant staff. The experiment was thus designed to be a domain independent study of effects of mild, acute hypoxia on cognitive performance. However, the test were carefully selected to map to cognitive functions which are most sensitive to mild hypoxia.
- The literature review and the experiment focused on cognitive effects of mild, acute hypoxia. Health effects and physiological effects were not considered or included, other than for health purposes (screening prior to participation and monitoring during the experiment).
- The space with 15% O_2 at FKA is 3.000 m^2 over three floors. This mean that employees working under the 15% O_2 hypoxic conditions undertake some level of physical activity moving around inside that space as part of their work. When more physically demanding work is to undertaken, the oxygen level is temporarily increased to normal levels (i.e. 21% O_2) to avoid the risks associated with physical and cognitive reactions due to physical activity under hypoxic conditions. Nevertheless, conducting a study where the hypoxic effects on cognitive performance are studied under a combination of physical rest and some level of physical performance would provide relevant information. To ensure a safe and reliable experimental environment, it was however not possible to establish controllable conditions offering space for a relevant level of physical activity. It should therefore be noted that a combination of physical activity and hypoxic conditions, for example in a crisis situation, may induce worse decrements on cognitive performance than at physical rest under the same level of hypoxic conditions.

4.3. Literature review of acute hypoxia

The literature review was focused on peer-reviewed scientific publications from conferences, journals, and textbooks. The search for relevant scientific publications utilized various search engines including for example Google, Medline, PsychINFO, and DTIC. More than 100 publications have been reviewed of which more than 60 are included in this report. The search efforts were focused on cognitive effects of mild, acute (i.e. without acclimatization) hypoxia, with a particular interest for studies conducted under normobaric conditions.

A number of delimitations concerning the literature review were made. Physiological and clinical health considerations were not covered to any larger extent in the review as they are sufficiently covered elsewhere (e.g. Ward, 2011; Davis, Johnson, Stepanek, & Fogarty, 2008). Further on, high altitude health and medicine (e.g.

Holmgren, 2007), and altitude sickness (e.g. Brundrett, 2002) are only briefly mentioned. The literature review did not consider cognitive effects of other types of challenges concerning air quality, e.g. effects of other gases, temperature, and humidity.

4.3.1. Overview of hypoxia and definitions

The term hypoxia refers to a state of "reduced oxygen" or "not enough oxygen", compared to normal breathing air. As oxygen is one of the most important components required for maintaining normal functioning of the brain, humans are vulnerable to the effects of oxygen deprivation, and physiological and psychological symptoms increase in severity with the degree of hypoxia. One scientifically and operatively relevant issue concerns what level of hypoxic exposure that leads to adverse and potentially safety challenging symptoms. Even relatively mild levels of hypoxia result in initial degradation of perceptual and cognitive functions such as impaired night vision, while moderate stages induce deficiencies on short- and long term memory functions, and severe stages that lead to rapid deterioration of central body functions. For example, a sudden exposure to a rapid decompression during flight at 12,000 meters (39,370 ft) will reduce the time of useful consciousness to approx. 10 to 20 s. During the history of aviation the lack of oxygen in flight has killed many military aircrews, and many crewmembers surviving such exposures can report on the experience of decreased physiological and psychological performance due to hypoxia (Ernsting, Sharp, & Harding, 1988).

Hypoxia can be caused by several factors including an insufficient supply of oxygen, inadequate transportation of oxygen, or the inability of the body tissues to use oxygen. The type of hypoxia of specific interest for this work is called hypoxic hypoxia, and refers to the effects of insufficient supply due to reduced oxygen levels in the air or breathing gas. This is the common form of oxygen shortage in aviation and mountain climbing. Hypoxic hypoxia occurs when breathing air due to the reduction in the partial pressure of oxygen as barometric pressure decreases with increasing altitude (hypobaric hypoxia) or if oxygen levels are reduced in the breathing gas at normal barometric pressure (normobaric hypoxia). Hypoxic hypoxia is caused by the absence of an adequate supply of oxygen in arterial and capillary blood. Although the percentage of oxygen contained in the air at for example 18,000 ft (5,486 m, 10.5% O_2) is identical to that at sea level, the amount of air the lungs take in with each breath contains only half the oxygen found at sea level, since the partial pressure of oxygen is reduced as an effect of the overall reduction in barometric air pressure.

This literature review focuses solely on hypoxic hypoxia, which is further on referred to as hypoxia, with a particular emphasis on hypoxia under normobaric conditions (further on referred to as normobaric hypoxia). The list below clarifies some of the terms relevant to the further reading of this report.

- **Normoxia/normoxic:** refers to exposure of normal room air, consisting of (approx. ratios) 20.95% O_2, 78.08% nitrogen (N_2), and 0.93% argon (the remaining 0.04% is a mixture of carbonoxide (CO_2), neon (Ne), helium (He), metan gas (CH_4), krypton (Kr), and hydrogen (H).
- **Normobaric:** refers to barometric air pressure equal to the standard barometric air pressure at sea level (1,013.25 hPa).
- **Hypobaric:** refers to barometric air pressure below (lower than) the standard barometric air pressure.

- **Hyperbaric:** refers to barometric air pressure above (higher than) the standard barometric air pressure at the sea level.

Appendix A presents a conversion table with corresponding altitudes in ft and m, and oxygen levels. Table 1 below present the stages of hypoxia as proposed by Woodrow & Webb (2011), which is a popular taxonomy frequently referred to in the scientific literature on hypoxia.

Table 1. *Woodrow & Webb's (2011) stages of hypoxia.*

Stage of hypoxia	Equivalent altitude	Arterial blood oxygen saturation (SaO_2) [2]
Indifferent	0-10,000 ft (0-3,048 m)	95-90%
Compensatory	10,000-15,000 ft (3,048-4,572 m)	90-80%
Disturbance	15,000-20,000 ft (4,572-6,096 m)	80-70%
Critical	20,000-23,000 ft (6,096-7,010 m)	70-60%

Woodrow & Webb (2011) consider 0-10,000 ft as the indifferent stage of hypoxia. However, there are research findings indicating that the signs and symptoms of the mild (compensatory) stage may be present already at 8,000 ft (e.g. Smith, 2005). In Table 2, Woodrow & Webb's stages have been adjusted to reflect these findings, some of them which even propose that the compensatory stage may initiate already at 5,000 ft (1,524 m, 17.2% O_2) (e.g. Smith, 2005). The adjusted table below, also includes the approximate oxygen level intervals for each stage of hypoxia.

Table 2. *Adjusted stages of hypoxia with mild (compensatory) stages starting at 8,000 ft (based on Woodrow & Webb, 2011)*

Stage of hypoxia	Equivalent altitude in ft (m)	Equivalent O_2 concentration (%)	Arterial blood oxygen saturation (SaO_2)
Indifferent	0-8,000 ft (0-2,438 m)	20.9-15.4%	100-90%
Mild (Compensatory)	8,000-15,000 ft (2,438-4,572 m)	15.4-11.7%	89-80%
Moderate (Disturbance)	15,000-20,000 ft (4,572-6,096 m)	11.7-9.7%	79-70%
Severe (Critical)	20,000-25,000 ft (6,096-7,620 m)	9.7-8%	69-60%

[2] Both the SaO_2 and SpO_2 measure is used in the report. Both are measurements of the saturation of haemoglobin with oxygen in arterial blood. The difference is how the measurement is conducted: SpO_2 (peripheral capillary oxygen saturation) represents indirect measurement using a finger probe, ear sensor, or similar device; SaO_2 (arterial oxygen saturation) is a direct measurement using a blood sample, such as an arterial blood gas analysis.

4.3.2. Effects of hypoxia

Numerous publications with summaries of the common effects of hypoxia can be found in the scientific literature. It can be concluded that there is a high overlap but not a complete consensus in the various listings, neither regarding the specific signs and symptoms nor which altitude/oxygen level they appear at. The descriptions of the most commonly cited publications are presented below, with effects from mild to severe hypoxia included. Effects of severe hypoxia during demonstrations/aircrew training events can be seen on for example www.youtube.com (search for "hypoxia"). Woodrow & Webb's (2011) listing of signs and symptoms of hypoxia are reflected in Table 3 (signs) and Table 4 (symptoms).

Table 3. *Objective symptoms of hypoxia (signs observable by others).*

Objective symptoms (signs observable by others)
Cyanosis (blue fingernails and lips)
Decreased reaction time
Euphoria (unusually happy) or belligerence
Impaired judgment
Increased respiration (increased depth/rate of breathing)
Mental confusion
Muscle incoordination
Unconsciousness

Table 4. *Subjective symptoms of hypoxia (self-observable).*

Subjective symptoms (self-observable)
"Air hunger" or oxygen want
Apprehension (worried or nervous)
Dizziness
Fatigue
Headache
Hot and cold flashes

Subjective symptoms (self-observable)
Lightheaded or dizzy sensation
Nausea
Tingling in fingers and toes
Visual impairment (e.g. blurred/tunnel vision, dimming of light or colour distinction)

Ernsting, Sharp, & Harding (1988) list the following signs and symptoms of acute hypoxia:

- Personality change
- Lack of insight
- Loss of judgement
- Feelings of unreality
- Loss of self-criticism
- Euphoria
- Loss of memory
- Mental incoordination
- Muscular incoordination
- Sensory loss
- Cyanosis (appearance of a blue or purple coloration)
- Hyperventilation, with signs and symptoms:
  - Dizziness
  - Light-headedness
  - Feeling of apprehension
  - Neuromuscular irritability
  - Paraesthesia of face and extremities (sensation of tingling, tickling, prickling, pricking, or burning of the skin)
  - Carpopedal spasm (a spasmodic contraction of the muscles of the hands and feet)
- Semi-consciousness
- Unconsciousness
- Death

Ernsting et al. (1988) also summarizes the cognitive and perceptual effects of acute hypobaric hypoxia in the following categories:

- Psychomotor Function
  - Eye-hand coordination impaired by 10,000 ft (3,048 m, 14.2% O_2), even for well-learned tasks.
  - Choice-reaction time impaired significantly by 12,000 ft (3,658 m, 13.2% O_2).
  - Muscular incoordination increases from 15,000 ft (4,572 m, 11.7% O_2) and above.
  - Simple reaction time is affected only from 18,000 ft (5,486 m, 10.5% O_2) and above.
- Cognitive function
  - Performance at novel tasks may be impaired at 8,000 ft (2,438 m, 15.5 % O_2).
  - Memory is increasingly impaired from 10,000 ft (3,048 m, 14.2% O_2) and above.

- Visual function (Ernsting et al. (1988) does not include any altitude thresholds for this category)
    - Light intensity is perceived as reduced.
    - Visual acuity is diminished in poor illumination.
    - Light perception threshold is increased.
    - Peripheral vision is narrowed (i.e. tunnel effects).

Shender, Mattingly, Warren, Coleman, Askew, & Tucker (2013) describe that the onset of hypoxia symptoms often is unrecognized and that hypoxia can cause:

- Anxiety/Euphoria
- Breathing Difficulty
- Dizziness
- Fatigue
- Loss of Muscle Coordination
- Mental Confusion
- Nausea (a sensation of unease and discomfort in the upper stomach)
- Numbness
- Poor Judgment
- Tingling/Twitching
- Unconsciousness
- Visual Impairment

Stepanek, Cocco, Pradhan, Smith, Bartlett, Studer et al. (2013) describes the following range of hypoxic symptoms:

- Paraesthesia (sensation of tingling, tickling, prickling, pricking, or burning of the skin)
- Increased rate and/or depth of breathing
- Headache
- Drowsiness
- Tachycardia (i.e. heart rate that exceeds the normal range)
- Light-headedness
- Loss of muscle coordination
- Impaired vision

Smith (2013) has proposed the following hierarchy of hypoxic thresholds:

- 5,000 ft (1,524 m, 17.2% O_2): decrements to light sensitivity of the dark-adapted eye.
- 8,000 ft (2,438 m, 15.4% O_2): short- and long-term memory impairment.
- 10,000 ft (3,048m 14.2% O_2): complex hand-eye coordination impairment; decreased performance on previously learnt coding and conceptual reasoning tasks.
- 12,000 ft (3,658 m, 13.2% O_2): decreased performance on pursuit motor tasks; increased choice-reaction time on well learned tasks.
- 15,000 ft (4,572 m, 11.7% O_2): fine hand tremor reduces ability to make precise adjustments.
- 16,000 ft (4,877 m, 11.3% O_2): simple reaction time increased.

The U.S. Army Aeromedical Training Manual (Department of the Army, 2000) describes the symptoms of hypoxia, as presented in Table 5 below.

Table 5. *U.S. Army Aeromedical Training Manual summary on symptoms of hypoxia (Department of the Army, 2000).*

Altitude	**0-10,000 ft (0-3,048 m, 20.9-14.2% O_2)**	**10,000-15,000 ft (3,048-4,572 m, 14.2-11.7% O_2)**	**15,000-20,000 ft (4,572-6,096 m, 11.7-9.7% O_2)**	**20,000-25,000 ft (6,096-7,620 m, 9.7-8.0% O_2)**
Estimated Arterial Oxygen Saturation	99-90%	89-80%	79-70%	69-60%
Symptoms	Night vision impairment.	Drowsiness. Poor judgment. Impaired coordination and efficiency.	Impaired flight control, handwriting, speech, vision, and judgment. Decreased coordination, memory and sensation to pain.	Circulatory failure. CNS failure. Convulsions. Cardiovascular collapse. Death.

4.3.3. Effects of barometric pressure on hypoxia

Petrassi, Gaydos, Ramiccio, & Lynne Walters (2011) describe how, over the past 15 years, normobaric methods which does not use an altitude chamber have increased. These systems employ hypoxic gas mixtures to induce hypoxia, typically by reducing the fraction of oxygen by replacing it with increased nitrogen. This method has gained popularity for the study of hypoxia (e.g. Temme, Bleiberg, Reeves, Still, Levison, & Browning, 2013) and training demonstrations of hypoxia (Cable, 2003; Harmon, 2010; Westerman, 2004). Westerman's observations is based on 452 participants of hypoxia training sessions and his conclusion is that altitude simulation using the reduced oxygen breathing technique provides a safe, convenient and cost-effective way to familiarise pilots and other aircrew with the effects of hypoxia and their individual response to it.

One central question of interest for this review is whether the effects of normobaric hypoxia and hypobaric hypoxia differ, in other words whether there is an effect of barometric pressure on how signs and symptoms develop due to reduced oxygen partial pressure? The frequently cited work of Angerer & Nowak (2003) is often taken as evidence indicating that work in a confined space during normal barometric pressure, with 15% O_2 to 13% O_2, will elicit physiological reactions similar to those of acute exposure to the corresponding altitudes of 2,700-3,850 m (8,858-12,631 ft). Evetts, Hartley, Keane, Keegan, Simpson, Taylor et al. (2005) compared three different hypoxia inducing methods. They compared low oxygen level at normobaric conditions, with normal air at 25,000 ft (7,620 m) and a combined condition where both oxygen level and pressure were reduced. Their results indicate that the physiological and performance responses can be considered to be identical, but conclude that the combination of both reduced pressure and oxygen level has the advantage for training purposes that it provides experience of hypoxia as well as reduced environmental pressure.

In US Navy studies, hypoxia induced by hypoxic gas mixtures has been found physiologically equivalent to that induced by a hypobaric chamber (Vacchiano, Vagedes, & Gonzalez, 2004). Sausen, Wallik, Sobodnik, Chimiak, Bower, Stiney, & Clark (2001) also reported that breathing gas mixtures with reduced oxygen for inducing normobaric hypoxia in a group of twelve US Navy divers produced results comparable with hypobaric chamber training of hypoxia.

However, due to the fact that it is the altered partial pressure rather than the fraction of oxygen in the air that causes the effects of hypobaric hypoxia, the equivalence of hypobaric and normobaric hypoxia has been questioned, especially for physiological studies (e.g. Conkin & Wessel, 2008) and conclusive evidence is still lacking. Eiken, Gennser, Zuber, Linder, & Bergöö (2011) acknowledge this, but chooses to remain with the traditional perspective that frequency and severity of hypoxic symptoms are neither milder nor different during normobaric hypoxia as compared with hypobaric hypoxia.

On the other hand, Roach, Loeppky, & Icenogle (1996) has reported on a distinction in severity of physiological response between normobaric and hypobaric hypoxia, with less severe symptoms observed in normobaric hypoxia than in hypobaric. They conclude that this may be due to the fact that hypobaric hypoxic exposures result in lower alveolar oxygen partial pressures than normobaric hypoxic exposures.

4.3.4. Studies of cognitive effects of mild, acute hypoxic hypoxia

As the effects of severe hypoxia has been studied for many years and the focus of the current review is on milder forms and exposures only two examples of studies of severe hypoxia are provided here. Experimental results such as those reported by Malle, Quinette, Laisney, Bourrilhon, Boissin, Desgranges, Eustache, & Piérard (2013) demonstrating how working memory performance deteriorates under severe hypobaric hypoxia at 10,000 m (32,808 ft, 5.9% O_2) are for example still published, although the results cannot be regarded as new or unexpected. There is no doubt that severe hypoxia has very strong effects on both physiology and psychology of persons exposed. Westerman's (2004) reports on studies of hypoxia with 452 participants on a simulated altitude of 7,620 m (25,000 ft, 8.0% O_2) performing a number of psychomotor and cognitive tasks commonly used during hypoxia training demonstrations. The tests included simple computational problems, serial 7 subtractions, eye-hand coordination (e.g. draw a five-pointed star), semantic memory and visual-motor coordination (e.g. complete a spoken phrase by writing it in full on the sheet of paper), recent memory (e.g. memorise a 7 digit number that is presented vocally and write it down), graphic memory and coordination task (e.g. draw accurately 10 minutes to 7 on a clock face). Westerman's results show that although individual variations are evident, physiological adjustments of heart and breathing activity included a heart rate increase (9-65 beats per minute [bpm], with an average increase of 31 bpm), hyperventilation and cyanosis. 65% of the participants reported at least one of the hypoxia related visual symptoms. The majority of the participants (89%) showed disturbances of memory functions, with the test of serial 7 subtractions (immediate recall) being the most prevalent deficiency (64%). The test of delayed recall of a name and address, and the recall of a 7 digit number were also frequently impaired (47%), while graphic and semantic memory tests showed less frequent errors. Simple arithmetical errors were made by 46% of participants. Visual-motor coordination was impaired for 25% of the participants, who exhibited motor incoordination, jerkiness, illegible writing, and poor reproduction of geometric figures. Neuromuscular symptoms of tremor or twitching were noted in 17% of participants.

Concerning the topic of primary interest for this review, cognitive effects of mild hypoxic hypoxia, the results are more inconclusive. For example, Burtscher, Mairer, Wille, Gatterer, Ruedl, Faulhaber et al. (2012) and Smith (2013), the latter describing how the literature on hypoxia is conflicting for altitudes up to 10,000 ft (3,048 m, 14.2% O_2), which becomes evident from the findings presented below. Recent reviews including the cognitive effects of mild hypoxia have been conducted by Petrassi, Gaydos, Ramiccio, & Lynne-Walters (2011) and Petrassi, Hodkinson, Walters, & Gaydos (2012). Based on field studies and laboratory experiments in hypobaric chambers, many researchers (e.g. Bonnon, Noel-Jorand, & Therme, 1995; Woodrow & Webb, 2011) indicate that 10,000-12,000 ft (3,048-3,658 m, 14.2-13.2% O_2) is the zone in which cognition, sensory, physiological, and psychological functions begin to become significantly impaired due to hypoxia.

Balldin, Tutt, Dart, Whitmore, Fischer, Harrison et al. (2007) report on a study on the effects of extended exposure to mild hypoxia on cognitive function and visual acuity (unaided and with night vision goggles). Thirty participants were exposed to two 12 hr exposures, one at ground level and another at 10,000 ft (3,048 m, 14.2% O_2) altitude in a hypobaric chamber. Half of the participants performed moderate physical exercise. The exposure at 10,000 ft did not lead to any significant negative effects on cognitive function, although minor negative effects on night vision goggle performance under starlight conditions were found. The altitude exposure did not have a negative effect on unaided night vision performance under twilight lighting conditions. There was a slight increase in self-reported symptoms of headache, fatigue, and lack of concentration. The increased reports of headache at altitude could possibly indicate early symptoms of mild acute mountain sickness.

Angerer & Nowak (2003) reviews the health and performance effects of people exposed to short-term, intermittent hypoxia. Reduction to 15% O_2 and 13% O_2 in normobaric atmospheres is equivalent to the hypobaric atmospheres found at 2,700 m and 3,850 m altitudes. When acutely exposed, a healthy person responds from within min up to hr with increased ventilation, stimulation of the sympathetic nervous system, increased heart rate, increased pulmonary-circulation resistance, reduced blood plasma volume, and increased production of red blood cells. Acute mountain sickness (AMS) occurs frequently at these oxygen partial pressures, but the full syndrome is rare if continuous exposure is limited to a maximum of 6 hr. Mood, cognitive abilities, and psychomotor functions may be mildly impaired in these conditions, but Angerer & Nowak describe data as being inconclusive. They conclude that preliminary evidence suggests that working environments with low oxygen concentrations at a minimum of 13% O_2 and normal barometric pressure do not impose a health hazard, provided that precautions are observed by relevant medical examinations and limitation of exposure times.

Early and influential but also disputed results from hypobaric hypoxia in a hypobaric chamber were presented by Denison, Ledwith, & Poulton (1966) who examined the combined effects of altitude and exercise on a mental orientation test. It was concluded that the altitude threshold for deterioration in mental functions may be as low as 1,524 m (5,000 ft, 17.6% O_2), based on observed performance on a spatial orientation task (Manikin test). The conclusion from Denison et al. was that acute hypoxia appeared to have an effect on the early stages of learning although it did not impair performance once a task had been learned. Fowler, Paul, Porlier, Elcombe, & Taylor (1985) replicated the conditions of the experiment by Denison et al. but did detect the same effects of hypoxia. Fowler et al. concluded that the minimum altitude at which hypoxic performance decrements can be detected is greater than 2,438 m (8,000 ft, 15.4% O_2) and they raised doubts about the 'task novelty' conclusion in the work of Denison et al. Similarly, Paul & Fraser examined the ability of 144 participants to learn new tasks at low altitude in a hypobaric chamber and measured performance in spatial orientation, serial choice reaction time, and logical reasoning tasks at sea level and at altitudes of between 1,500-3,660 m (5,000-12,000 ft, 17.6-13.6% O_2). They reported that the ability to learn new tasks such as spatial orientation (Manikin), serial choice reaction time, and logical reasoning was not impaired by mild acute hypoxia at simulated altitudes of up to 3,660 m (12,000 ft, 13.6% O_2).

In a series of experiments, a group of researchers studied three two-week hypoxic exposures (Gustafsson, Gennser, & Örnhagen, 1997; Gustafsson, Gensser, Örnhagen, & Derefeldt, 1998; Linde, Gustafsson, & Örnhagen, 1998) with the purpose of investigating effects of hypoxia as a fire prevention method aboard submarines. In these studies, a total of 22 participants, with submarine experience and between 20 and 28 years old, were exposed to various levels of normobaric hypoxia with exposure to 14% O_2 and 15% O_2 levels for up to 10 days as well as 13% O_2 for up to 24 hr with intervening periods of normal air. In each of the experimental conditions, eight subjects were divided into two teams working six hr shifts around the clock. Throughout the experiment, an extensive battery of physiological, cognitive, and psychomotor tests, as well as mood and symptom questionnaires were administered. In many of the tests, performance improved over time as a result of practice effects, despite the reduced oxygen levels. No reduction in cognitive or psychomotor performance was observed at any of the oxygen levels examined. Oxygen levels down to 14% were well tolerated for up to 10 days. Cognitive and psychomotor performance levels were maintained during the 24 hr long exposures to 13% O_2. At 13% O_2 the participants reported an increase in subjective symptoms of hypoxia. Based on their literature review, the conclusion by Gustafsson et al. (1997) was that acute exposures (< 1 hr) appear to cause a larger decrement in mental functions than prolonged exposures, indicating that an acclimatization to hypoxia takes place, and that learning of a novel task appears to be the cognitive function most sensitive to hypoxia. Their conclusion after their comprehensive experiment was that exposure to normobaric hypoxia with a 14% O_2 and 15% O_2 level for several days did not affect psychomotor or cognitive performance significantly. The same conclusion was valid also for exposure to 13% O_2 for 24 hr, with no significant decrements in performance although for some participants the subjective discomfort ratings indicated symptoms of hypoxia.

In a similar submarine related study by Knight, Cymerman, Devine, Burse, Fulco, Rock et al. (1990), the performance of 11 participants under two conditions of normobaric hypoxia was studied, with 13% O_2 and 17 % O_2. From this study it was concluded that normobaric 17% O_2 level was acceptable, but normobaric 13% O_2 level produced short-term decrements in cognitive functioning (timed arithmetics) and mood ratings, and moderate symptoms of hypoxia for some individuals.

Piehl Aulin, Svedenhag, Wide, Berglund, & Saltin (1998) found that exposure to normobaric hypoxia on an altitude of 2,000 m (6,562 ft, 16% O_2) with six participants and 2,700 m (8,858 ft, 14.8% O_2) with nine participants for 12 h per day while maintaining a physical training load did not show a negative effect on the reported mood states among the participants.

In Degia, Emegbo, Stanley, Pedlar, & Whyte (2003) eight participants were exposed to normobaric hypoxia (2,500 m, 8,200 ft, 15.2% O_2), normobaric normoxia (as placebo), and normal air conditions in a randomized order for three consecutive nights in a hypoxic tent and tested on a number of cognitive tests. No significant differences were found for the two hypoxic conditions and the conclusion was that the hypoxic conditions did not have an effect on psychomotor or cognitive performance.

In a study Pavlicek, Schirlo, Nebel, Regard, Koller, & Brugge (2005) assessed the effects of hypobaric hypoxia with 21 participants exposed to altitudes of 3,000 m (9,842 ft, 14.8% O_2) or 4,500 m (14,763 ft, 11.7% O_2) for two hours, and found no significant change in word fluency and three word-association tasks.

Fulco & Cymerman (1988) reviewed published decrements in human performance versus altitude and arterial oxygen blood saturation. They describe how loss of attention and visual acuity at arterial saturation of less than 90% but greater than 85% can be critical in military settings.

Watson, Martin, McAnally, Smith, & Emonson (2000) studied the effects of normobaric hypoxia on auditory sensitivity up to simulated altitudes of 3,700 m (12,139 ft, 13.2% O_2), but did not find any decrements in the sensitivity to sound.

In Markou, Smyrnis, Daskalopoulos, Giatas, Kodounis, Chimonas et al. (2001), 15 military cadets and an equivalent control group performed cognitive performance tasks at sea level and under normobaric hypoxic conditions where adjustment of the gas mix was kept constant to a level of oxygen saturation of the blood (SaO_2) at 90%. The finding of this study was that the hypoxic conditions did not affect the performance of the cognitive tasks.

Noble, Jones, & Davis (1993) reported on an experiment studying the effects of decreased oxygen saturation on cognitive performance. Two groups of participants completed four mental tasks after breathing normal air or a hypoxic gas mixture so that arterial oxygen saturation for the hypoxic group reached 80%. For the group exposed to hypoxia cognitive performance decreased and reaction times increased. Based on this Noble et al. conclude that the hypoxic condition could result in decreased cognitive performance, although they acknowledge that the lack of difficulty of the tests may have influenced the results.

Cable (2003) presented results from 27 hypoxic related aviation incident reports, concluding that the majority of hypoxic symptoms in these incidents appeared between 10,000 and 19,000 ft (3,048-5,791 m, 14.2-10.1% O_2).

According to a report from the U.S. Naval Medical Research Unit (NAMRU, 2011) four hypoxia related mishaps with loss of pilots and aircraft occurred from 2000 to 2011, and that within the same period of time 113 hypoxia-related hazard reports were filed by the pilot community of the fighter aircraft F/A-18.

In Hewett, Curry, Rath, & Collins (2009), the subtle effects of mild hypoxia were studied with 50 participants exposed to five simulated altitudes: sea level, 8,000 ft, 10,000 ft, 12,000 ft and 14,000 ft (0-4,267 m, 20.9-12.2% O_2) with performance evaluated with a cognitive test battery. Although the oxygen saturation levels showed that the participants were hypoxic, there were no statistically significant changes in reaction time or accuracy due to increasing altitude.

Smith (2005) described symptoms of hypoxia in helicopter aircrew when operating under 8,000 ft (2,438 m, 15.4% O_2). In surveys from 53 crew members, 76% reported having experienced symptoms of hypoxia (difficulty with calculations, light-headedness, delayed reaction time, mental confusion) with symptoms appearing as low as 6,500 ft (1,981 m, 16.3% O_2). Smith's conclusion was that aircraft cabin hypoxia at 5,000-8,000 ft (1,524-2,438 m, 17.2-15.4% O_2) probably impairs aspects of human performance and may degrade crew resource management for aircrew.

Bartholomew, Jensen, Petros, Richard Ferraro, Fire, Biberdorf et al. (2009) studied the hypoxic effects of moderate altitudes, at 12,500 ft and 15,000 ft (3,810-4,572 m, 13.0-11.7% O_2), on short-term memory. Seventy-two junior pilots were tested with a number of cognitive tasks. The participants were then exposed to hypoxia for 90 min. Participants performed a 30-min vigilance task while listening to an audiotape with instructions to recall radio calls prefaced by their assigned call sign. Half of the radio calls contained a high memory load (with at least four pieces of information), and the other half contained low memory loads (no more than two pieces of information). No effects of hypoxia were found on performance on the vigilance task. However, for read-backs during high memory load, significant deficits in recall were observed at both 15,000 ft and 12,500 ft, whereas no effect of altitude was observed on recall of read-backs with low memory loads. These results indicate that, at altitude, short-term memory was impaired for the read-backs requiring a larger amount of information to be recalled.

In Pighin, Bonini, Savadori, Hadjichristidis, & Schena (2014) and Pighin, Bonini, Savadori, Hadjichristidis, Antonetti, & Schena (2012) effects of hypoxia on loss aversion are studied in response to the fact that they consider the amount of research on the impact of hypoxia on judgment and decision making to be lacking. In their experiments they found that 26 participants increased their risk taking concerning gambling decisions, indicating an increased risk taking behaviour when breathing a 14.1% O_2 concentration. Their conclusion was thus that mild hypoxia may push individuals to be less cautious in decisions that involve trade-offs between gain and loss. Pighin et al. (2012) found that while mildly hypoxic, the participants' tendency to avoid risk to secure a certain gain and to seek risk to avoid a certain loss was affected. The locus of the effect of hypoxia on the reflection effect was in the domain of losses. The mild decrease in oxygen level increased risk seeking concerning losses, but showed no effect concerning gains.

In Legg, Hill, Gilbey, Raman, Schlader, & Mündel (2014) 25 participants were exposed to mild, normobaric hypoxia (8,000 ft, 2,438 m, 15.4% O_2), and were tested with a range of cognitive and psychomotor measures. Among their findings was that the working memory span decreased after 90 min of exposure. They also found that reasoning speed was longer, particularly for harder logical operations (syllogisms, i.e. a formal argument in logic that is formed by two statements and a conclusion which must be true if the two statements are true) that were invalid or conflicting. Reasoning accuracy was not affected. Due to these results their conclusion was that mild hypoxia, equivalent to normal airline cabins, can affect complex decision-making in novel and stressful situations.

Hovis, Milburn, & Nesthus (2013) quoted that pilots in United States' airspace are permitted to fly without supplemental oxygen at altitudes up to 12,500 ft (3,810 m, 13.0% O_2). At higher altitudes the pilots' perceptual and cognitive abilities can become impaired, which can affect safety unless supplemental oxygen is used. For example, colour perception is usually affected in a hypoxic environment. Although there is a fair degree of individual variability of hypoxic symptoms, losses in colour discrimination typically begin to occur at oxygen concentrations that are equivalent to an altitude of 8,000 ft (2,438 m, 15.5% O_2) under light conditions typical during night-time flying. The discrimination losses begin to occur at normal daytime light conditions as the altitude increases above 10,000 ft (3,048 m, 14.2% O_2), with more marked losses occurring above 13,000 ft (3,962 m, 12.7% O_2) regarding the ability to separate certain colours.

Deussing, Artino, Anthony, & Folga (2010) surveyed 566 military pilots concerning in-flight hypoxia events. The results indicate that as many as 79% of hypoxic events go unreported, which suggest that the problem of hypoxia in aviation is greater than indicated by official statistics.

From an experiment with acute exposure to a simulated altitude of 3,048 m (10,000 ft, 14.2% O_2), Vaernes, Owe, & Myking (1984) reported impaired performance on seven out of nine different neuropsychological and operational tests. Testing was performed when reaching 3,048 m, as well as every second hr for a total of 6.5 hr. Apart from impaired performance on the tests, subjects in this study reported headache, weakness, and by some also dizziness.

In Shukitt-Hale, Banderet, & Lieberman (1998) symptoms, mood and performance changes during exposure to hypobaric hypoxia conditions were studied. Twenty-three male participants were exposed to three different levels of hypobaric hypoxia: 500 m (1,800 ft, approx. 20.6% O_2), 4,200 m (13,800 ft, approx. 12.7% O_2), and 4,700 m (15,500 ft, approx. 11.5% O_2). Exposure to altitude has a significant effect on symptoms, moods, and cognitive as well as motor performance. Adverse changes increased with higher altitudes (an effect was observed on all measures at 4,700 m, whereas only some showed an effect at 4,200 m) and usually with longer durations. The results show that some symptoms, mood ratings, and performance levels showed a significant negative effect after a few hours of exposure to hypobaric hypoxia, and the severity of these effects dramatically increased when exposed to 4,700 m compared to 4,200 m.

4.3.5. Individual differences and interaction effects

Numerous factors, internal or external to the individual, contribute to the total hypoxic effects experienced by an individual. DeHart & Davis (1996) mentions a number of individual factors that affect acclimatization and individual effects to reduced oxygen levels, such as physical fitness, emotional state, alcohol consumption, tobacco consumption, presence of drugs or medication in the system, nutritional status, level of fatigue, and the degree to which the individual has been acclimatized to the environment. For these reasons, the effects of hypoxia exhibit rather large individual variations with regard to symptoms. Examples of external factors can be onset rate, temperature and physical exertion. Thus numerous factors contribute to the total effect of exposure to hypoxic air.

Several additional factors may influence a person's susceptibility to hypoxia, and alter the pattern of symptoms and signs (e.g. Küpper et al., 2009), including:

- Physical activity: physical exercise reinforces the effects of hypoxia.
- Temperature: tolerance to hypoxia decrease with reduced temperature.
- Diseases and illness: the additional metabolic load imposed by illness and the effects of some diseases increases susceptibility to hypoxia.
- Drugs: many pharmacologically active substances impose effects similar to those of hypoxic hypoxia, and can hence affect hypoxic conditions; medicine containing antihistamine components are particularly likely to worsen hypoxic reactions, as is alcohol.

Küpper et al. (2009) describes how occupational exposure to mild hypoxic conditions normally does not constitute a risk, but mention five important factors that must be taken into account for the differentiation and the risk profile of exposure to hypoxia:

- Altitude or equivalent altitude (i.e. O_2 level)
- Duration of exposure
- Altitude profile/acclimatization (intermittent hypoxia included)
- Workload under hypoxic conditions
- Native highlanders vs. native lowlanders

Lawler, Powers, & Thompson (1988) studied the effects of hypoxic conditions on more physically fit vs. less physically fit individuals. They found that the more fit individuals (marathon runners) experienced greater detriments in their cognitive performance. Ando, Hatamoto, Sudo, Kiyonaga, Tanaka, & Higaki (2013) studied interaction effects of physical exercise during exposure to hypoxia, and found no interactions effects on psychomotor performance. Woorons, Mollard, Pichon, Lamberto, Duvallet, & Richalet (2007) reports that arterial blood saturation decreases faster for trained men as compared to untrained men (no cognitive testing was conducted).

Angerer & Nowak (2003) lists a number of diseases that could results in an interaction effect with hypoxia and suggest “screening out” persons with pre-existing heart disease, carotid artery disease, peripheral vascular disease, seizure history, diabetic complications, anaemia, recent surgery, and several additional conditions. Persons who have suffered from a stroke in their history, who got radiation therapy of neck or head, with large foramen oval, or single pulmonary artery, may be at increased risk when exposed to altitude, even if they do not experience any related symptoms at low altitude.

Schega, Peter, Törpel, Mutschler, Isermann, & Hamacher (2003) presents inconclusive results from a pilot study concerning the effects of intermittent hypoxia on cognitive performance of persons between 60-70 years of age, but conclude that interactions effects between age and age related diseases can reinforce reactions to hypoxia.

Temme, Bleiberg, Reeves, Still, Levison, & Browning (2013) studied the effects of latent deficits due to mild traumatic brain injury (concussion) by using normobaric hypoxic stress. Using the ANAM cognitive test battery they found how the cognitive performance of the participants in their experiment, who previously had suffered concussions, deteriorated more rapidly during hypoxic stress although performance under normal conditions was equal to the performance of a control group.

Nesthus, Garner, Mills, & Wise (1997) studied interaction effects between smoking (which affects the oxygen carrying capacity of the blood) and mild hypoxic hypoxia and compared a group of nine smokers with nine non-smokers on four normobaric simulated altitudes between sea level and 12,500 ft (3,810 m, 12.9% O_2). They measured several physiological indicators as well as perception and cognitive performance. In their results the smokers exhibited higher error rates and false alarms for some monitoring tasks, and showed statistically significantly poorer tracking task performance than the non-smoker group.

4.3.6. Summary of literature study

The conclusion from the literature review is that only minor, if any, cognitive effects may be observed at the oxygen level (15% O_2) that is currently used as a fire prevention method in some spaces of the nuclear power plant of FKA, assuming that personnel are properly health screened, that the exposure schedules are followed, and that the guidelines for personal health (e.g. no smoking) and physical activity inside the hypoxic environment are adhered to (e.g., low physical activity). Table 6 provides a summary of the results from a number of selected publications that explicitly address cognitive effects of hypoxia in the range from 13-17% O_2. It is is intended to summarize cognitive effects that has been observed and may be present within this interval of reduced oxygen. Please note that not all references, e.g. Smith (2013) and Ernsting et al. (1988), reflect experimental results, since some of them represent literature reviews or meta-analyses of studies of hypoxia.

Table 6. *Summary of scientific findings of decrements on cognitive performance as an effect of mild, acute hypoxia in the interval of 13-17% O_2 concentration.*

Cognitive effects of mild, acute hypoxia with O_2 levels at 13-14% (approx. 12,000-10,000 ft; 3,650-3,050 m)	
Effects	*Reference*
Choice-reaction time impaired significantly by 12,000 ft (3,658 m, 13.2% O_2).	Ernsting et al. (1988)
Decreased performance on pursuit motor tasks; increased choice-reaction time on well learned tasks.at 12,000 ft (3,658 m, 13.2% O_2):	Smith (2013)
10,000-12,000 ft (3,048-3,658 m, 14.2-13.2% O_2) is concluded to be the zone in which cognition, sensory, physiological, and psychological functions begin to become significantly impaired due to hypoxia.	Noel-Jorand et al. (1995)
At 13% (12,500 ft, 3,810 m) oxygen the participants reported an increase in subjective symptoms of hypoxia.	Gustafsson et al. (1997, 1998)
13% (12,500 ft, 3,810 m) oxygen level produced short-term decrements in cognitive functioning (timed arithmetic performance) and mood ratings, and moderate symptoms of AMS for some individuals.	Knight et al. (1990)
26 participants increased their risk taking concerning gambling decisions, indicating an increased risk taking behaviour when breathing a 14.1% O_2 concentration (approx. 9,800 ft; 3,000 m).	Pighin et al. (2012)
Cognitive effects of mild, acute hypoxia with O_2 levels at 14-15% (approx. 10,000-8,500 ft; 3,050-2,600 m)	
Effects	*Reference*
Eye-hand coordination impaired by 10,000 ft (3,048 m, 14.2% O_2), even for well-learned tasks.	Ernsting et al. (1988)
Memory is increasingly impaired from 10,000 ft (3,048 m, 14.2% O_2) and above.	Ernsting et al. (1988)
Complex hand-eye coordination impairment; decreased performance on previously learnt coding and conceptual reasoning tasks at 10,000 ft (3,048m 14.2% O_2):	Smith (2013)
Impaired performance on seven out of nine different neuropsychological and operational tests at 3,048 m (10,000 ft, 14.2% O_2)	Vaernes et al. (1984)
Cognitive effects of mild, acute hypoxia with O_2 levels at 15-16% (approx. 8,500-7,000 ft; 2,600-2,100 m)	
Effects	*Reference*
Performance at novel tasks may be impaired at 8,000 ft (2,438 m, 15.5 % O_2).	Denison et al. (1966)
Short- and long-term memory impairment already at 8,000 ft (2,438 m, 15.4% O_2).	Smith (2013)

In surveys from 53 crew members, 76% reported having experienced symptoms of hypoxia (difficulty with calculations, light-headedness, delayed reaction time, mental confusion) with symptoms appearing as low as 6,500 ft (1,981 m, 16.3% O_2).	Smith (2005)
Working memory span decreased after 90 min exposure at 2,438 m (8,000 ft, 15.4% O_2). Reasoning speed was longer, particularly for harder logical operations. Reasoning accuracy not affected.	Legg et al. (2014)
Losses in colour discrimination typically begin to occur at oxygen concentrations that are equivalent to an altitude of 8,000 ft (2,438 m, 15.4% O_2) under light conditions typical during night-time flying.	Hovis et al. (2013)
Cognitive effects of mild, acute hypoxia with O_2 levels at 16-17% (approx. 7,000-5,000 ft; 2,100-1,500 m)	
Effects	*Reference*
5,000 ft (1,524 m, 17.2% O_2), decrements to light sensitivity of the dark-adapted eye.	Smith (2013)

In Appendix B-Appendix F (Section 9.1-Section 9.6), the publications included in the literature review have been grouped with regard to whether they are based on studies under normobaric or hypobaric conditions, or a combination of the two. Publications representing literature surveys and textbook chapters form their own group. Information concerning oxygen levels or simulated altitudes, number of participants, types of measures used, and major results is also included, where available.

Overall, the literature review indicates that the research question concerning cognitive effects of mild, acute normobaric hypoxia is warranted and that current research findings available in the scientific literature indicate that subtle effects may be present already at oxygen levels of 16-17%. It is also concluded that current research results are inconclusive, partly due to that a wide range of conditions and measures have been studied and partly since a relatively low number of experimental studies specifically have studied cognitive effects of mild, acute hypoxia under normobaric conditions.

4.4. Measurement of cognitive performance

Given the complexity of human cognition, it is challenging to develop measures with the same properties as the measures of the natural sciences. The measurement of psychological phenomena typically contains a number of trade-off judgments and has received intense attention throughout the history of psychology. Concerns regarding the validity, reliability, and sensitivity of the measures must be managed before a specific measure is chosen in any study.

Validity refers to the extent by which a variable measures what it is intended to measure. Reliability can be defined as the proportion of the total variance of a measure that is true variance. An obtained measure or score is assumed to be the sum of a true measure and an error component. Test-retest reliability refers to the capability of a measure to repeat the same results when the exact conditions are replicated on two or more separate occasions. The sensitivity of a measure is closely related to its reliability (i.e. the relationship between true and total variance). It indicates a measure’s capability to distinguish between the effects of different experimental conditions that participants are exposed to. Sensitivity is an important criterion, and critical for the selection of measures, especially in a study as the present one, where any effects from hypoxia are presumed to be subtle.

A number of computerized science-based tests of cognitive performance were evaluated during the experiment set-up phase. The primary candidates evaluated were:

- ANAM, Automated Neuropsychological Assessment Metrics (www.vistalifesciences.com)
- King-Devick test (kingdevicktest.com)
- Lumosity (www.lumosity.com)
- CogScreen (www.cogscreen.com)
- CogMed (www.cogmed.com)
- SynWin (www.activityresearch.com)
- Aptitude tests at Hogrefe/Psykologiförlaget (www.hogrefe.se)

The batteries in the list above all test basic cognitive functions and are associated with different psychometric and practical preconditions. After evaluation of test design, theoretical foundation, practical details, and pricing, the King-Devick test (K-D test) and the ANAM test library were chosen for the experiment. Both tests are described in further detail in Section 5.2.

Based on the literature review, eight subtests from ANAM's total of 22 tests were selected. The eight subtests map to those cognitive functions that could be expected to potentially be affected by the hypoxic condition (described in further detail in Section 5.2.2).

Subjective ratings or answers to surveys, questionnaires and interview questions can provide very valuable data concerning psychological phenomena. However, they have to be carefully designed and tested in order to ensure validity and reliability. Physiological measurements (i.e. measures of the body functions such as heart rate) are an important source of data, depending on the scope of a study. Physiological measures can sometimes be used as psychophysiological measures (i.e. the changes in physiological measures are used as indicators for psychological phenomena, e.g. mental workload). For the current study physiological measurement of heart rate (HR) and peripheral capillary oxygen saturation (SpO_2) was primarily used for health monitoring.

4.5. Hypothesis

The underlying research question and the rationale for the current study was whether there are any cognitive decrements due to mild, acute hypoxia under normobaric conditions. The current scientific literature, extensively studied during the literature review, provides somewhat inconclusive evidence, e.g. Petrassi, Gaydos, Ramiccio, & Lynne Walters (2011). This is partly due to that a wide range of conditions and measures have been studied and partly since a relatively low number of experimental studies specifically have studied cognitive effects of mild, acute hypoxia at or near 15% O_2 under normobaric conditions. However, despite the few findings at 15% O_2 listed in Table 6, the vast majority of the studies included in the overall literature review suggest that any observable hypoxia induced decrements on cognitive performance at 15% O_2 under the exposure schedule currently applied at FKA would be subtle, *if at all present*.

The hypotheses to be tested through under the conditions of the experiment was formulated as:

- H0. There is no negative effect on cognitive performance due to hypoxic exposure at 15% O_2.
- H1. There is a negative effect on cognitive performance due to hypoxic exposure at 15% O_2.

5. Method

5.1. Participants

5.1.1. Participant characteristics

In order to be eligible to participate in the experimental part of the study, the participants had to have a level of education from upper secondary school/high school (in Swedish: "Gymnasieutbildning") with corresponding knowledge of English, in Sweden or abroad, and be between 25 and 65 years of age, with recruitment focused on participants over 30 years of age. Participants had to pass a health screening survey[3] that was administered during the recruitment phase. The health screening survey was inspected and approved by a qualified flight and diving surgeon, with extensive experience of human reactions to exposure of hypoxic conditions (e.g. hypoxia demonstration training for military and civilian flying personnel).

5.1.2. Sampling procedures

After approval of the experiment by the Regional Ethics Review Board in Stockholm (Etikprövningsnämnden, www.epn.se), persons in the city of Linköping, fulfilling the required participant characteristics, were contacted via e-mail or telephone. No participants were in any type of dependency toward the research team, or any other people or organizations involved in this research. 48 persons were approached and a total of 18 were available, willing, and eligible to participate.

5.1.3. Sample size, power, and precision

The a priori decided sample size was determined through power analysis with the tool Gpower 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). With an accepted statistical power of .80 (which is a frequently applied a priori power value) for detecting effect sizes of .20 (which represent a small effect size, which means that subtle differences of cognitive performance should be detected), for a repeated measures within-factors design, and with a correlation between repeated measures of .76[4], the sample size should at a minimum be 16 participants for analysis through a repeated measures ANOVA, and at a minimum 20 participants for a repeated measures MANOVA. With this information at hand, and in relation to the budget constraints of the study, 18 participants was deemed sufficient in terms of power.

[3] The health screening survey assessed (yes/no) the following factors: anaemia, heart/lung disease, nervous system disease (e.g. epilepsy), stroke, high blood pressure, diabetes, dyslexia, colour blindness, and if the potential participant was: smoking; feeling healthy; using any medication; or under pregnancy.
[4] The value of .76 was calculated through a mean calculation of the test-retest correlation for the eight selected ANAM measures that is available in ANAM's technical manual (University of Oklahoma, 2013).

5.2. Measures and covariates

5.2.1. King-Devick test

The K-D test has been developed to detect subtle cognitive effects from concussion, sleep deprivation, Parkinson's disease and hypoxia. According to the developers, the K-D test provides the capability to detect pre-symptomatic cognitive impairment, i.e. it detects cognitive decrements before symptoms are perceived by, or observed at, the participant. The K-D test has for at least one other study been successfully utilized (Stepanek et al., 2013).

The K-D test was evaluated by the research team during a hypoxia demonstration training session at the facility that was later used for the conduction of this experiment. During this initial evaluation of the K-D test, 14 participants were exposed to a nitrogen-balanced breathing gas mixture with 9% O_2, as part of their commercial airline pilot training. The test satisfied the psychometric requirements of the study concerning reliability, validity, and sensitivity. The conclusion from this evaluation of the K-D test was that it captured negative effects of hypoxia at 9% O_2, and was appropriate and efficient to include in the experiment design.

The K-D test is based on sequential rapid number reading aloud, with performance based on completion time and number of errors. The procedure involves reading aloud a series of single digit numbers from left to right on three test cards and requires less than two minutes to administer, including one demonstration card and three actual test cards per test occasion (see Figure 1 for an example of K-D test stimuli). Participants are asked to read aloud the numbers on each card from left to right as quickly as possible without making any errors. The sum of the three test card times constitutes the completion time for the entire test. The number of errors made in reading the test cards is also recorded by research personnel. Ipads were used to administer the digitized K-D test, with automatic recording of completion times while any errors were noted by the research team on a score sheet. The participants completed the test four times during training in normal room air without mask, once during baseline while breathing normal room air through the mask, and four times during exposure #1 and #2 to the experimental condition with 15% O_2 provided through the mask (3, 10, 60 and 110 minutes into the exposure on both occasions), and twice during exposure #3 to the experimental condition (3 and 10 minutes into the exposure), and finally once during the post-test while breathing normal room air through the mask. The test took approximately two minutes to complete per test occasion, including practical handling of the Ipads. The participants completed the tests one at the time, with time separated start of exposure to the hypoxic gas, i.e. the first participant received hypoxic gas approximately 6 min before the third to ensure that they were all tested at the right time in relation to the start of exposure (i.e. after 3 min).

Regarding performance changes as effect of training (i.e. practice effects), K-D test performance has been found to stabilize after the four training runs. During the training session prior to experimental measurements, each participant were accordingly taking the K-D test four times in order to familiarize and reach asymptotic performance.

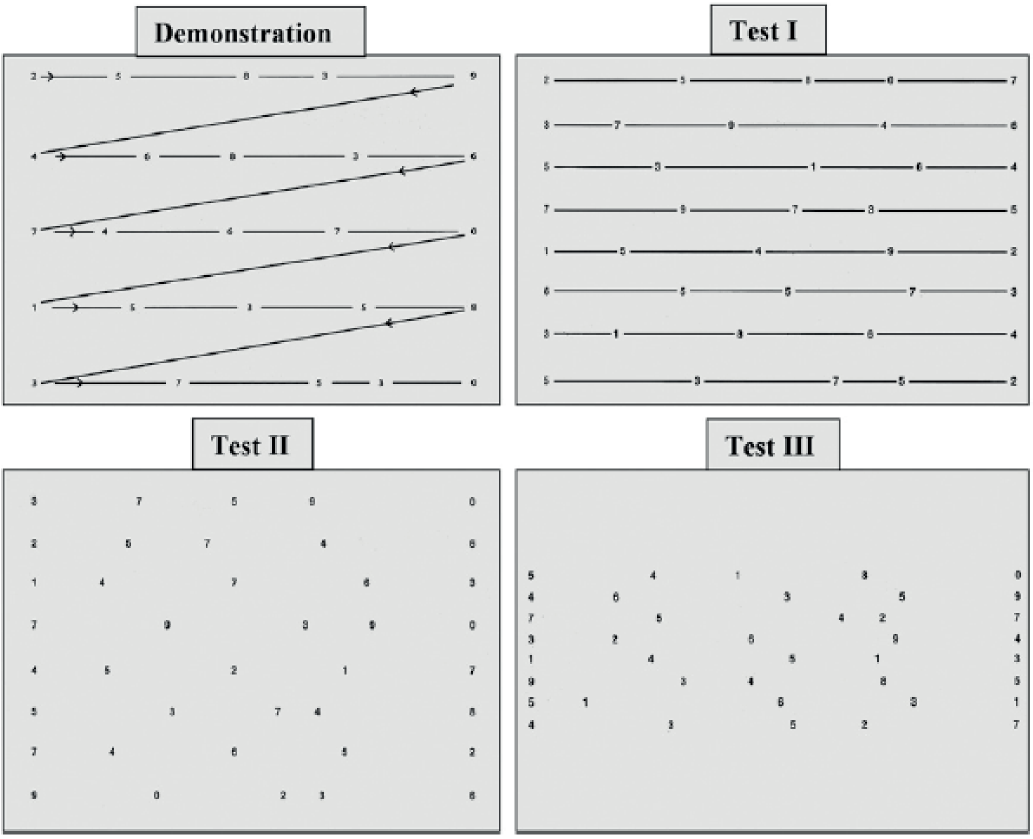

Figure 1. Example of King-Devick test stimuli.

5.2.2. Automated Neuropsychological Assessment Metrics

In order to create a richer dataset and complement the K-D test, the ANAM test battery was also used during the experiment to measure cognitive performance. ANAM is an abbreviation for the Automated Neuropsychological Assessment Metrics and represent a library of cognitive tests. ANAM is developed by Vista Life Sciences Inc., and also include data extraction and presentation tools for custom analysis and data management as well as a performance report tool for reporting on individual test with comparisons to previous assessment sessions. ANAM tests neuropsychological functions, including many cognitive functions, and encompass a total of 22 individual tests sensitive to changes in cognitive domains such as:

- Attention
- Concentration
- Reaction time
- Memory
- Processing speed
- Decision-making
- Executive functions

ANAM has been developed for more than 30 years and is cited in more than 300 peer-reviewed scientific publications. Extensive studies concerning reliability, validity and important psychometric issues concerning the different subtests have been performed during this time (University of Oklahoma, 2013). ANAM test development has followed the principle of identifying relatively discrete cognitive, perceptual, neuropsychological, or human performance domains, then implementing simple but effective tests of those domains while minimizing factors that might add error variance. ANAM tests have been used to study injury (e.g. trauma, blast), illness (e.g. degenerative disease), exposure (e.g. toxin), risk factors (e.g. heat/cold, sleep loss, fatigue) and interventions (e.g. medication, rehabilitation). It has also been used for studies of hypoxia, e.g. Balldin et al. (2007). Out of ANAM's 22 available subtests, eight were carefully selected based on the results from the literature review. The selected subtests were chosen to map to cognitive functions which based on previous research studied in the literature review could be plausibly expected to exhibit the highest sensitivity to mild, acute hypoxia.

Brief descriptions[5] of the eight selected subtests are provided below. The tests were administered on modern Lenovo Yoga laptop computers with Windows 7, 13.3 inch screens, and with usb-wire mouse as the input device (keyboard was only used for entering name, gender, and age on the ANAM demographics screen at the first training occasion). The participants completed the ANAM test simultaneously on three separate laptops.

Running memory - Continuous performance test

The Running memory - Continuous performance test (CPT) taps attention, concentration, and working memory. During the test single characters are presented on the display in a rapid sequence. The user presses designated buttons to indicate if the displayed character matches or does not match the preceding character. Figure 2 exemplifies the nature of CPT.

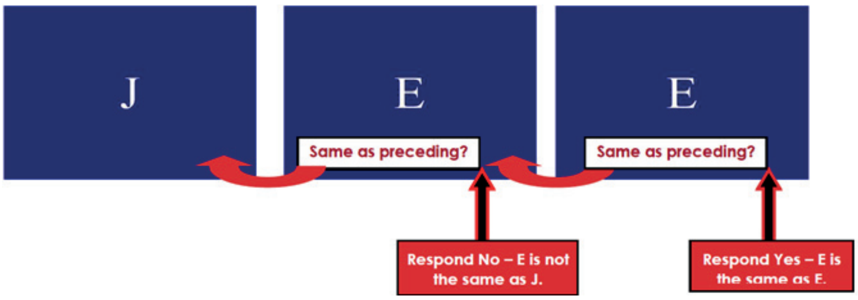

Figure 2. Example of Running memory - Continuous performance test stimuli.

2-Choice reaction time

The 2-choice reaction time test (2CH) taps attention and processing speed when making a simple choice. During the test a series of stimuli of a "*" or "o" is presented on the display. The users are instructed to respond as quickly as possible by pressing the designated button for each stimulus as it appears. Figure 3 exemplifies the nature of 2CH.

[5] The descriptions of the selected ANAM subtests are based on text and graphics from ANAM's Technical Manual (University of Oklahoma, 2013).

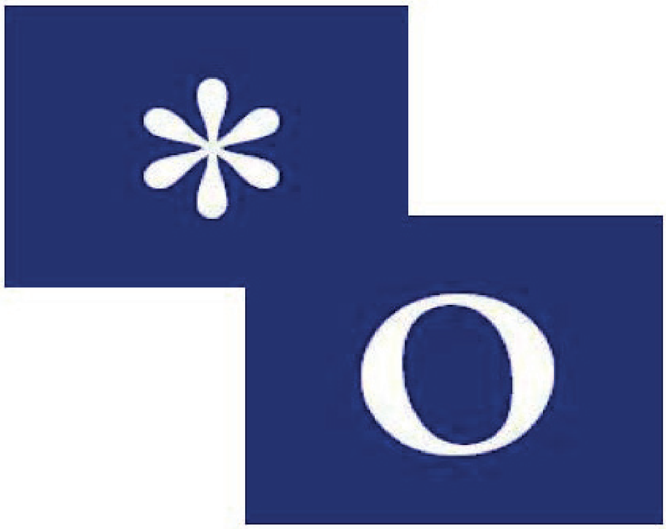

Figure 3. Example of 2-Choice reaction time test stimuli.

Logical relations

The Logical relations test (LRS) taps reasoning and verbal syntax. The user evaluates the truth of a statement (e.g. "& comes after #") describing the order of two symbols presented on the display (e.g. "& #"). The user presses designated buttons to indicate whether the statement is true or false. Figure 4 exemplifies the nature of LRS.

Figure 4. Example of Logical relations test stimuli.

Pursuit tracking

Results of the Pursuit tracking test (PRT) are used as an index of visuo-motor control. The user is instructed to move the mouse so that the mouse pointer tracks a moving circle with a "+" inside. The pointer should remain inside the circle and be kept as close to the "+" as possible. Figure 5 exemplifies the nature of PRT.

Figure 5. The Pursuit tracking test stimuli.

Matching to sample

The Matching to sample test (M2S) taps spatial processing and visuo-spatial working memory. The user is presented to a pattern produced by eight shaded cells in a 4x4 sample grid. The sample is then removed and two comparison patterns are displayed side by side. One grid is identical to the sample grid and the other grid differs by one shaded cell. The user is instructed to press a designated button to select the grid that matches the sample. Figure 6 exemplifies the nature of M2S.

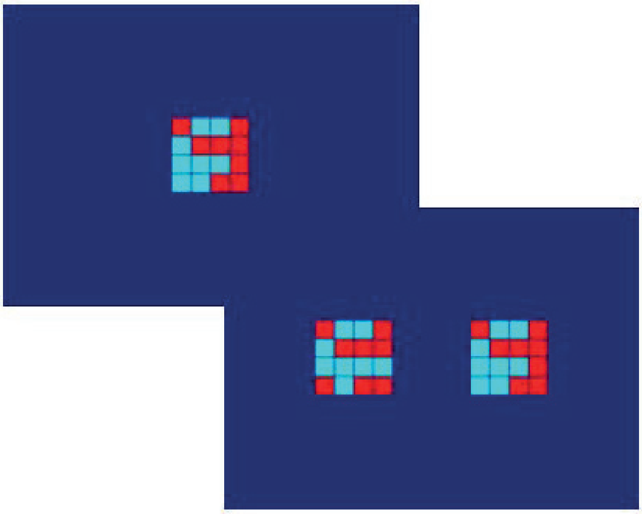

Figure 6. Example of Matching to sample test stimuli.

Mathematical processing

The Mathematical processing test (MTH) taps basic computational skills, concentration, and working memory. During this test, an arithmetic problem involving three single-digit numbers and two operators is displayed (e.g. "4 + 8 - 5 ="). The user presses buttons to indicate whether the correct answer to the calculation is less than five or greater than five (the result is never equal to five). Figure 7 exemplifies the nature of MTH.

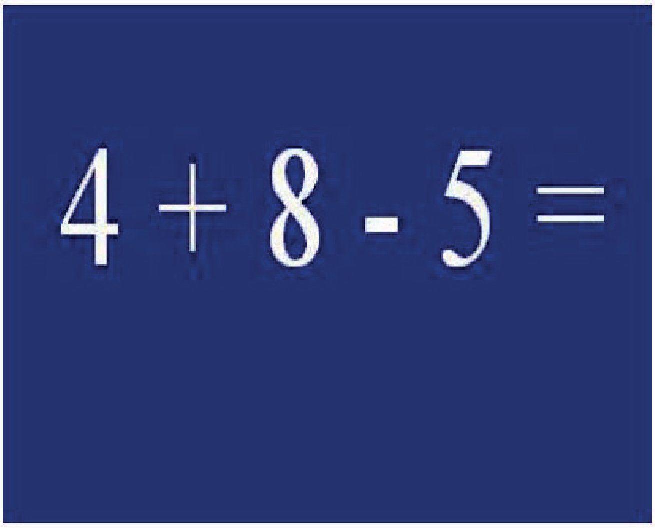

Figure 7. Example of Mathematical processing test stimuli.

Manikin

The Manikin test (MKV) taps three-dimensional spatial rotation ability, left-right orientation, problem solving, and attention. During the test a man is displayed on the screen holding a ball in one hand. The man is standing upright or upside down and either facing toward or away from the user. The user is instructed to indicate which of the man's hands is holding the ball displayed at the bottom of the screen by pressing designated buttons. Figure 8 exemplifies the nature of MKV.

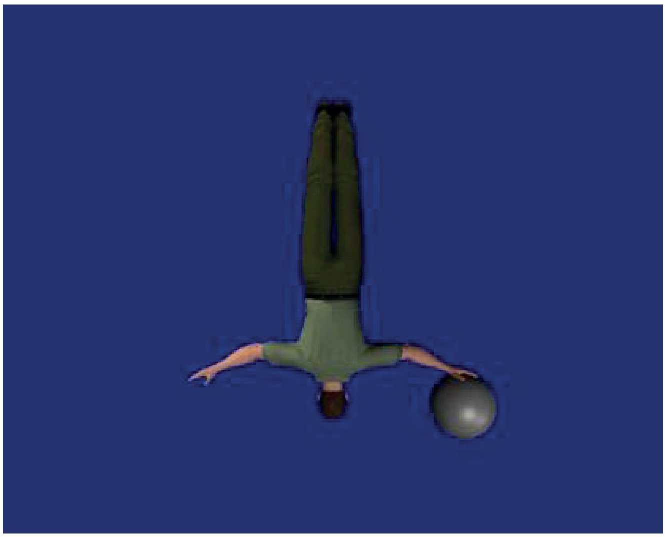

Figure 8. Example of Manikin test stimuli.

Switching

The Switching test (SWW) taps directed attention and executive function in addition to the abilities evaluated by the individual tests of mathematical processing and the manikin test as this a combination of tests. One type of problem is presented on the display and the user responds as appropriate for the given test. Problems from the other type of test is then presented and the user switches between the two problem types. Figure 9 exemplifies the nature of SWW.

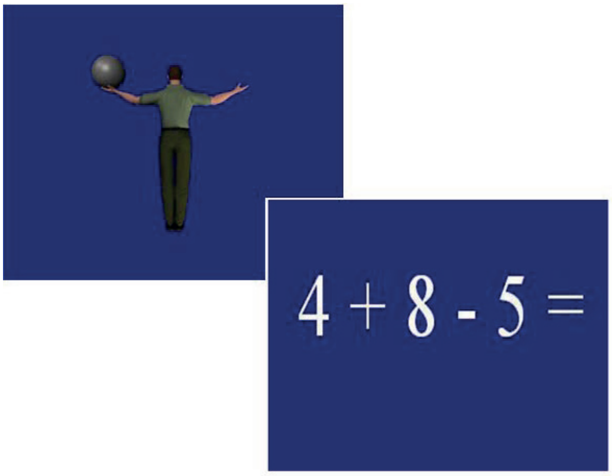

Figure 9. Example of Switching test stimuli (combination of the Manikin and Mathematical processing stimuli).

Choice of variables for analysis

ANAM produces an extensive set of different variables from the different subtests and an analytical choice with regard to which variables to analyse was necessary. For example, the 2-Choice Reaction Time test produces 20 variables of different types. The variables 'Speed[6]' and 'Accuracy/Percentage Correct' together form the variable 'Throughput[7]' which was selected as the performance measure variable. Good performance on this subtest is to quickly and accurately classify all the 40 stimuli (i.e. "*" or "o" choices), hence the choice of the Throughput variable. For the Logical Relations test, 18 variables are produced and similarly 'Throughput' was chosen as the primary measure. The availability of variables is similar for the other subtest and Throughput (combining correct answer and speed) was chosen for all tests except for Pursuit Tracking. Since Throughput is not an applicable variable for Pursuit Tracking, Mean Distance from the centre of the pursuit target was selected as the variable for analysis.

Practice effects

It is common practice in psychological research to train participants on the tests prior to measurement under experimental conditions in order to minimize the potential error variance due to learning, i.e. practice effects. While ANAM tests are rather straightforward, experience with any test in a short time span may result in increased performance due to practice effects. ANAM has specifically been designed to meet the needs of researchers who test cognitive performance in long-term (6 to 12 months), short-term (daily to weekly), and within session repeated-measures assessments (hours). The system has a pseudo-randomization procedure that permits creation of near-limitless alternate versions of stimuli sets, thus allowing tests to be used for performance monitoring and in repeated-measures designs (University of Oklahoma, 2013). The practice effects of ANAM results have been studied by a number of researchers, e.g. Benedetto, Harris, & Goernert (1995) who demonstrated minimal learning after three trials across six tests from the ANAM library. The largest performance changes occurred upon second administration with minimal improvement following the second session. Later, Harris & Goernert (1997) recommended a minimum of four training sessions to remove the variability in results due to familiarity with the tests. The recommendation from the test developer (Vista

[6] Speed is here defined as number of Responses per minute (=60,000/MeanReactionTime)
[7] The full definition of Throughput is: Number of correct responses per unit of available response time [=NumCorrect / ((NumCorrect+NumIncorrect)*MeanReactionTime + NumLapse*Timeout)]

Life Sciences) is at least two training sessions prior to data collection under experimental intervention is initiated, which was adopted during this experiment. It should be mentioned however that following the training session where each participants worked through all eights subtests of the selected ANAM battery twice they were baseline tested. In that regard they had been exposed to the battery three times, twice in training and once in baseline, prior to the first test under the experimental condition.

5.2.3. Fatigue, discomfort, and hypoxic symptoms

Subjective ratings of fatigue, discomfort, and hypoxic symptoms were collected at ten occasions throughout the experiment. See the research design section for a representation of when these ratings were administered.

Modified Samn-Perelli fatigue scale

The Samn-Perelli fatigue scale (Samn & Perelli, 1982) was translated to application in Swedish (Figure 10) and used during the experiment to assess the fatigue of the participants throughout the course of the day.

Vilket påstående nedan stämmer bäst med hur du känner dig just nu? ***(Which statement below maps best how to you feel right now?)***	
Beskrivning ***(Description)***	**Skattning** ***(Rating)***
I toppform, helt vaken (*Fully alert, wide awake)*	1
Pigg, uppmärksam, men inte på topp *(Very lively, responsive, but not at peak)*	2
Okej, ganska pigg *(Okay, somewhat fresh)*	3
Lite trött, inte helt pigg *(A little tired, less than fresh)*	4
Ganska trött, orkar inte anstränga mig mer *(Moderately tired, feeling let down)*	5
Mycket trött, mycket svårt att koncentrera mig *(Extremely tired, very difficult to concentrate)*	6
Helt utmattad, kan inte agera ordentligt, redo att falla ihop *(Completely exhausted unable to function effectlively, ready to drop)*	7

Figure 10. Modified Samn-Perelli fatigue scale (adopted and modified based on Samn & Perelli, 1982).

GEISTT discomfort scale

The discomfort scale (Figure 11) was developed for this experiment, by the research team.

Känner du något obehag? *(Do you feel any discomfort?)*	**JA *(Yes)* NEJ *(No)***
Vad orsakar obehaget? *(What causes the discomfort?)*	
Ange hur kraftigt obehaget är genom att markera en siffra nedan: **_(Indicate the severity of the discomfort by marking a number below)_**	
Beskrivning *(Description)*	**Skattning *(Rating)***
Inte märkbart *(Not noticeable)*	1
Ibland märkbart *(Occasionally noticeable)*	2
Konstant märkbart *(Constantly noticeable)*	3
Ibland störande *(Occasionally annoying)*	4
Konstant störande *(Constantly annoying)*	5
Kliande irriterande *(Ithcing and irritating)*	6
Störande tryck *(Concerning pressure)*	7
Gör ont *(Hurts)*	8
Smärtsamt *(Painful)*	9

Figure 11. GEISTT discomfort scale.

Hypoxic symptoms rating scale

Based on the list of typical hypoxic symptoms provided in Ernsting et al. (1988), Shender et al. (2013), and Stepanek et al. (2013) a simple rating scale was developed to capture any perceived occurrence of hypoxic symptoms (Figure 12).

Känner du av något/några av följande symptom? **_(Do you perceive any of the following symptoms?)_**	**Skattning (Rating)**
1= Känner inte alls ***(Do not perceive at all)*** **2= Känner någonting** ***(Perceive something)*** **3= Känner tydligt** ***(Perceive clearly)*** **Symptom** ***(Symptoms)***	
Onormal känsla i huden, t.ex. stickande, kittlande eller pirrande (*Unnormal sensation of pricking, tickling or tingling in the skin)*	1 2 3
Ökad frekvens eller djup i andning *(Increased rate and/or depth of breathing)*	1 2 3
Huvudvärk *(Headache)*	1 2 3
Dåsighet *(Drowsiness)*	1 2 3
Hjärtklappning (*Heart rate that exceeds the normal range)*	1 2 3
Upprymdhet	1 2 3

(Light-headedness)	
Försämrad muskelkoordination *(Impaired muscle coordination)*	1 2 3
Försämrad syn *(Impaired vision)*	1 2 3
Känsla av ”icke närvarande” *(A feeling of “non-presence”)*	1 2 3
Förändrad ljuskänslighet/upplevd ljusnivå (*Changes in light sensitivity/perceived light intensity)*	1 2 3
Minnesproblem *(Memory impairments)*	1 2 3
Koncentrationsproblem *(Concentration impairments)*	1 2 3
Lätt distraherad *(Easily distracted)*	1 2 3
Illamående *(Nausea)*	1 2 3

Figure 12. Hypoxic symptoms rating scale.

5.2.4. Physiological measurements

Heart Rate (HR) and peripheral capillary oxygen saturation (SpO_2) was continuously measured through pulse-oximetry (Masemo Radical) when participants were seated in the hypobaric chamber. The sensor was placed on the index or middle finger of the non-dominant hand throughout baseline testing, the three experimental exposure sessions, and post-testing. All measurement occasions were conducted during seated rest, without any physical activity.

5.2.5. Hypobaric chamber and masks

The experiment was conducted in the hypobaric chamber at the Flight Physiological Centre (FPC) at Malmen Air Force Base, operated by QinetiQ Sweden AB (http://www.fpc.qinetiq.se). FPC provided the facility and operating personnel as a subcontractor to GEISTT AB. The hypobaric chamber at FPC is typically used for hypoxia demonstration training of pilots and other aircrew, as well as various medical treatments. During the experiment, normobaric conditions were used, hence the chamber was not pressurized and the chamber door was left open at all times. FPC and the hypobaric chamber was selected since it offers an effective, reliable, and safe infrastructure for the provision of the breathing gas mixtures and physiological monitoring as well as access to medical expertise and equipment in case of emergency.

Hypoxia was induced by providing a hypoxic premixed nitrogen balanced (i.e. oxygen is replaced by more nitrogen) gas mixture of 15% O_2 (accepted error marginal of +-0.5%; partial pressure O_2 [P_iO_2] = 104.6 mmHg; prior to delivery, the gas mixture was controlled by the provider Spiromec, and again by QinetiQ FPC upon delivery), which is equivalent to the P_iO_2 at approximately 9,000 ft or 2,700 m, through the breathing mask (Hypoxico Exercise Mask). The masks were of oro-nasal type (covering mouth and nose; see Figure 13) and the gas was provided with overpressure to hinder, in case any leaks would occur, room air from entering the mask (which would increase the oxygen level under the experimental exposure).

Figure 13. Participants during an experiment session in the hypobaric chamber at QinetiQ Flight Physiology Centre.

5.3. Research design

The study was designed as a within-participant experiment with training, baseline, three experimental exposures to a reduced oxygen level (15% O_2), and a post-test as described further in Figure 14. The independent variable was oxygen level with two conditions: normal room air (21% O_2) and a nitrogen-balanced breathing gas mixture with 15% O_2 (i.e. the experimental condition). During baseline and post-testing the participants were seated in the chamber breathing normal room air through the mask, and during the exposure to the experimental condition breathing the 15% gas mixture through the mask. All participants received the same instructions and exposures to the experimental condition. The switching from normal room air and the experimental breathing gas mixture, and vice versa, while breathing through the mask induced an initial slight change in taste, temperature, and pressure. Therefore, and for research ethical reasons, a decision was made to keep the participants informed of which gas they were currently breathing, to ensure their focus on the tests rather than the breathing gas. However, it should be noted that this could possibly have induced a slight risk for a bias among the participants, in the regard that they, intentionally or not, would be biased to invest more effort to perform better during hypoxic exposure. The last of the experimental exposures was 45 minutes, i.e. shortened with respect to the work schema of three 2-hours sessions at FKA. This was done in order to avoid risk of fatigue effects due to a long experiment, as training and post-testing also required time. The difference in data collection versus three full 2-hours sessions was minor, with only two K-D test occasions being excluded.

Occasion name and duration	Training 60 min	Baseline 30 min	Exposure 1 120 min	Break 15 15 min	Exposure 2 120 min	Break 30 30 min	Exposure 3 45 min	Post test 30 min
Oxygen level and mask	21% O_2 no mask	21% O_2 mask	15% O_2 mask	21% O_2 no mask	15% O_2 mask	21% O_2 no mask	15% O_2 mask	21% O_2 mask
ANAM occasion	A1	A2	A3		A4		A5	A6
King-Devick occasion	KD1-KD4	KD5	KD6 KD7 KD8 KD9		KD10 KD11 KD12 KD13		KD14 KD15	KD16
Fatigue, discomfort and symtoms ratings	F1	F2	F3 F4 F5		F6 F7 F8		F9	F10
Physiological measures		HR & SpO_2	HR & SpO_2		HR & SpO_2		HR & SpO_2	HR & SpO_2

Figure 14. A schematic representation of the research design showing data collection occasions and experimental conditions.

Markings of test and rating occasions in Figure 14 provide information concerning the order in which the participants completed them, rather than exact times, which is instead described in detail under Sections 5.2.1-5.2.4.

6. Results

6.1. Participant flow

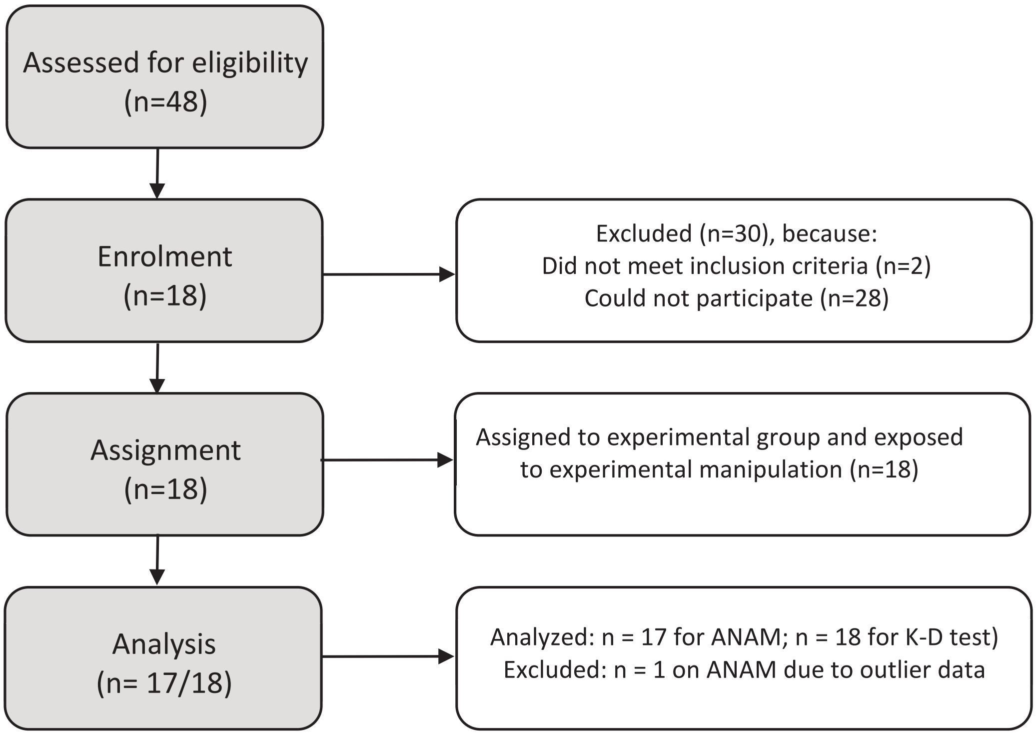

Figure 15. Participant flow through the stages of experiment preparation and execution[8].

6.2. Recruitment

The data collection of the experimental phase of the study was conducted during a total of six days in May and June 2014. The recruitment of the participants was conducted during the weeks before each specific day of the experiment, with participant confirmation about a week in advance. The participants received monetary compensation for their participation, approximately comparable to a day's salary for persons with their level of education.

6.3. Data analysis and statistics

The statistical software package SPSS 22 was used for all statistical analyses presented in the report. The a priori type 1 error rate was $p < .05$, with Bonferroni correction used for repeated measures. The statistical hypothesis testing based on data from K-D test and ANAM test results is focused on comparisons across the baseline and experimental condition exposures. Hence data from the training occasions and the post-testing occasion are omitted in the further presentation of descriptive data and

[8] The outlier data is further described in section 4.3.

statistical analyses of K-D test and ANAM test results throughout this section. However, that data is presented and discussed in the analysis of practice effects, see Appendix 9.7.

6.3.1. Normality of data

Both statistical univariate and multivariate normality as well a set of assumptions concerning linearity, outliers, and multicollinearity of the ANAM data, which is a prerequisite for the planned statistical analyses, was initially assessed though inspection of different types of graphs and plots. Descriptive data for the K-D test and ANAM tests are provided below, at the appropriate subsection. Figure 16 shows an example of a histogram showing the univariate normality of one of the ANAM variables.

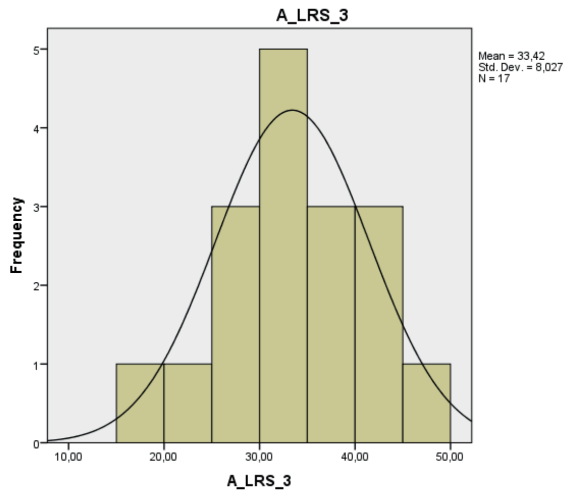

Figure 16. Data normality example.

The distributions in terms of skewness and kurtosis of the data for the variables are not all as normal as in the figure, but the data from ANAM was also analysed for statistical normality through the Kolmogorov-Smirnov statistic. A few ANAM variables did not meet the Kolmogorov-Smirnov criteria, especially variables relating to the Pursuit tracking test which were positively skewed and with high kurtosis. Nevertheless they were retained in the further analysis since the pattern on these variables was homogenous, and the impact of their non-normality was assumed to be minor.

The statistical normality of the K-D test time variables was assessed in a similar way. The amount of errors variables from the K-D test (KD1_error – KD16_error) were also inspected, without any expectation that they would be normally distributed. Four of them contained no errors and for most of the other K-D occasions only one error was recorded. The monitoring for errors was for this experiment mainly considered to be a control against careless reading, and the K-D time variables were of primary interest. The K-D test error rates are thus not considered further in this analysis.

6.3.2. Missing data

Due to the strict procedural discipline during the experiment no missing data exists. At two occasions the ANAM test had to be restarted due to technical problems, but the two individual participants could quickly complete the data collection due to the ANAM software's capability to resume aborted testing at the exact place where problems occurred.

The ANAM results from one participant was removed as that participant's data file indicated test throughput being 4-10 times faster than the rest of the participants. This participants did not stand out as faster than the rest during the data collection. The reason for this outlier data is unknown, however it is not plausibly related to any effects of hypoxia on cognitive performance.

6.3.3. Demographics

The mean age of the participants (6 female and 12 male) were 36.2 years with a standard deviation of 7.7. The mean age of the population in the nuclear power plant of FKA is 44.3 years.

6.3.4. Physiological measurements

Peripheral capillary oxygen saturation (SpO_2) and Heart Rate (HR) of the participants were constantly monitored when they were seated in the hypobaric chamber, with data recorded twice per minute. Table 7 presents descriptive data for each participant regarding minimum SpO_2 as well as maximum and mean HR during the exposures to 15% O_2. Figure 17 presents an example curve of SpO_2 and HR for one participant during baseline and the transition into the first exposure to the experimental condition.

Descriptive data SpO_2 and HR

The mean SpO_2 during exposure to the experimental conditions was 92.7 with a standard deviation of 1.4. The mean heart rate was 76.2 with a standard deviation of 9.8.

In Table 7, the participants' individual descriptive statistics from the physiological measures are provided. Note that the minimum SpO_2 values and max HR values are the extremes and often only reached during a few seconds.

Table 7. *Descriptive statistics for physiological measures during exposure to 15% oxygen.*

Participant ID	Min SpO_2	Mean SpO_2	Max HR	Mean HR
1	90	94.9	95	80.2
2	88	94.2	95	75.9
3	87	92.5	97	75.5
4	89	90.0	96	76.0
5	89	94.8	107	84.0
6	87	93.3	108	89.2
7	87	91.6	80	60.6
8	86	90.8	101	75.8
9	85	91.4	120	90.7
10	84	92.1	103	77.5
11	90	93.7	83	60.9

Participant ID	Min SpO_2	Mean SpO_2	Max HR	Mean HR
12	86	91.7	70	57.4
13	89	91.9	84	68.3
14	88	93.9	105	75.1
15	88	94.4	116	91.6
16	90	92.2	95	81.1
17	91	93.2	87	76.5
18	90	91.9	88	74.4

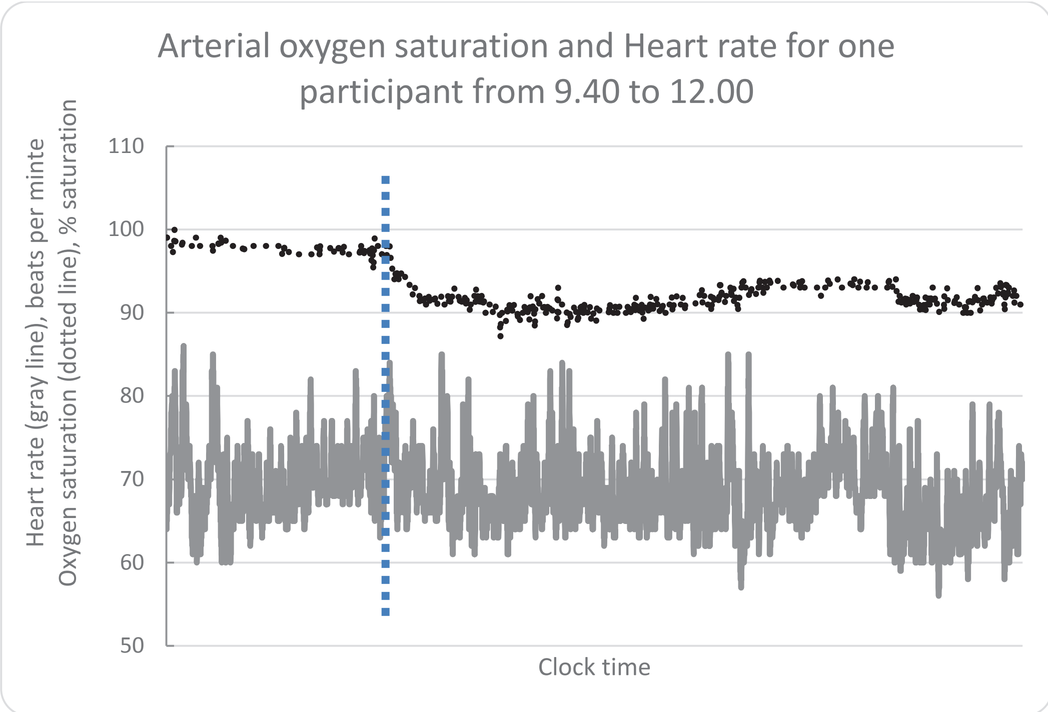

Figure 17. Demonstration of peripheral capillary oxygen saturation and heart rate for one participant during baseline testing (normal room air) and experimental exposure #1 (15% oxygen). The blue vertical line indicates the switch between normal air and 15% oxygen.

6.3.5. King-Devick test

Descriptive statistics King-Devick test

Descriptive data concerning the K-D test completion times are provided in Table 8. As previously described, data from the four training occasions (i.e. KD1-4_time) and the post-test occasion are excluded here, however they are included in the analysis of practice effects presented in Appendix 9.7.

Table 8. *Descriptive statistics for King-Devick test completion times in seconds.*

Occasion	N	Mean	Standard Deviation
KD5_time (Baseline)	18	46,20	6,18
KD6_time (Exposure 1, 3 min)	18	45,63	6,63
KD7_time (Exposure 1, 10 min)	18	44,03	6,33

Occasion	N	Mean	Standard Deviation
KD8_time (Exposure 1, 60 min)	18	45,08	7,11
KD9_time (Exposure 1, 110 min)	18	44,46	6,97
KD10_time (Exposure 2, 3 min)	18	44,67	6,09
KD11_time (Exposure 2, 10 min)	18	43,98	5,81
KD12_time (Exposure 2, 60 min)	18	44,50	5,98
KD13_time (Exposure 2, 110 min)	18	44,97	6,91
KD14_time (Exposure 3, 3 min)	18	43,38	6,05
KD15_time (Exposure 3, 10 min)	18	42,76	6,46

In Figure 18, the mean completion times for the K-D test are presented graphically.

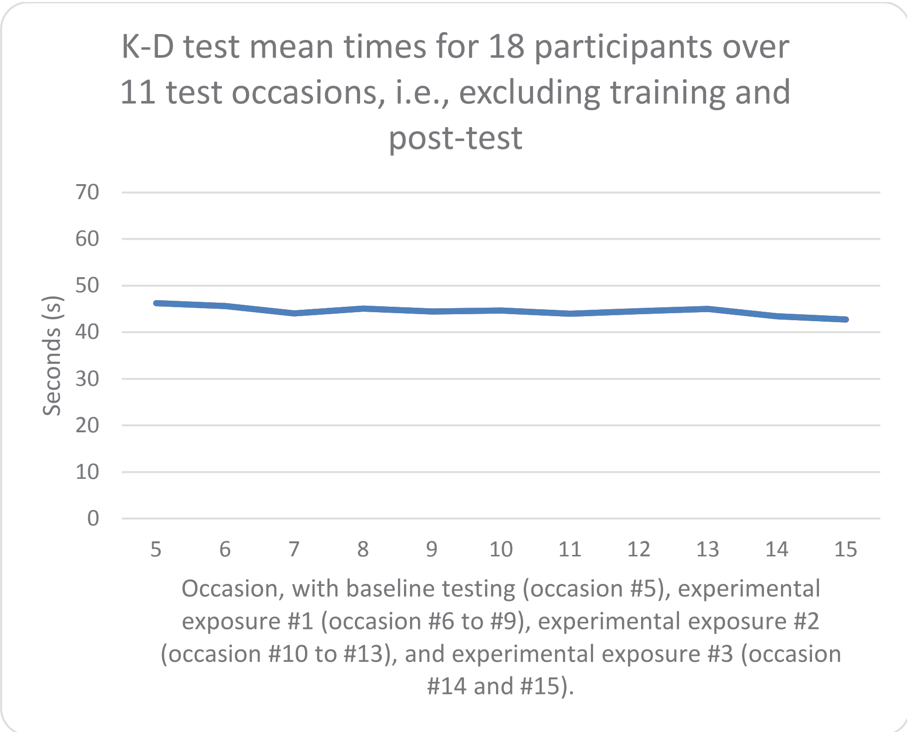

Figure 18. King-Devick test mean results across baseline and experimental testing.

Repeated measures ANOVA

A one-way repeated measures analysis of variance (ANOVA) was conducted to compare scores on the eleven K-D test occasions during baseline and the three exposures to the experimental condition (i.e. as described in Section 6.3, with the four training occasions and the post-test occasion excluded). The means and standard deviations are presented in Table 8. There was no significant effect for occasion (KD5-16_Time), Wilks' Lambda = .222, $F(11, 7) = 41.17$, $p = .148$. Hence, no statistically significant differences in performance on the K-D test across baseline (normal room air) and the three exposures to the experimental condition (nitrogen-balanced breathing gas mixture of 15% O_2) were observed.

Correlation with fatigue ratings

The relationship between K-D test completion times and the fatigue ratings was investigated using Pearson product-moment correlation. There was only an extremely weak correlation between the two variables, $r = -.099$, $n = 288$[9], $p = .093$[10].

6.3.6. Automated Neuropsychological Assessment Metrics

Analysis of variance (ANOVA) techniques is appropriate when there are two or more groups of data to compare. When the same participants are tested repeatedly, a repeated measures ANOVA would typically be an appropriate analysis method. For the analysis of ANAM results in this study that would mean a running series of ANOVAs to investigate differences for each test across all relevant test occasions. However, the use of a series of ANOVA's may inflate the risk of making a statistical type 1 error, which means by chance observing an effect caused supporting the rejection of the null hypothesis. The use of the more complex MANOVA technique (Multivariate Analysis of Variance) can then be used to take a more conservative approach, reducing the risk for type 1 error of rejecting the null hypothesis based on an effect caused by chance rather than the experimental condition.

MANOVA simultaneously examines several dependent variables, measured at the same point in time, across one or more independent variables. The repeated measures MANOVA that was used for the analysis of ANAM results explore several dependent variables at two or more occasions in a within-group analysis. The MANOVA combines several dependent variables into one composite dependent variable that is used for comparisons between occasions. In this specific case, it means that for each occasion it combines the scores of each dependent variable (i.e. the eight ANAM subtest variables) according to a highly complex statistical procedure. The results is that one composite dependent variable (called cognitive performance), based on the eight dependent variables (the eight cognitive ANAM subtests), is created for each test occasion and then compared across occasions. Mayers (2013) offer rather detailed, general descriptions of different kinds of MANOVA's and their underlying assumptions.

Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no serious violations noted. Based on this and the fact that the variables are conceptually related (they all represent measures of various though related cognitive functions), a one-way repeated measures MANOVA was selected as the appropriate initial statistical analysis for hypothesis testing based on the ANAM data. This means that one composite dependent variable (based on the eight dependent variables per test occasion) called cognitive performance was compared across the four occasions used for statistical hypothesis testing of the ANAM data. In the sections below, the analysis of variance of ANAM results across the experimental conditions (15% O_2) and normal room air (21% O_2) are presented.

[9] Since more than one K-D test completion time variable sometimes map against the same fatigue rating (see Section 5.2.3 for detailed description), the data file for this analysis had to be transposed which explains the reported of n = 288.

[10] Whether the fatigue rating is a continuous or ordinal variable can be discussed, However the Spearman rho correlation which is .12 with a significance of .041, and thus describes a similar results as the Pearson correlation in this case.

Descriptive data from ANAM testing

Table 9 presents descriptive data for the eight subtests of the ANAM test battery across four occasions (2 = baseline, 3 = experimental exposure #1, 4= experimental exposure #2, 5 = experimental exposure #3): running memory continuous performance test (variables A_CPT_2-5), 2-choice reaction time (variables A_2CH_2-5), logical relations (variables A_LRS_2-5), matching to sample (variables A_M2S_2-5), pursuit tracking (variables A_PRT_2-5), mathematical processing (variables A_MTH_2-5), manikin (variables A_MKV_2-5), and switching (variables A_SWW_2-5). During the training session the participants completed the ANAM test twice, but only the results from the last of the two training iterations are presented in the report, which is in accordance with ANAM routines.

Table 9. *Descriptive statistics for ANAM variables excl. training occasions and the post-test occasion.*

Variables	N	Mean	Standard Deviation
Running Memory Continuous Performance variables			
A_CPT_2	17	99,71	19,61
A_CPT_3	17	104,73	20,73
A_CPT_4	17	103,65	21,09
A_CPT_5	17	109,27	18,16
2-Choice Reaction variables			
A_2CH_2	17	138,92	18,14
A_2CH_3	17	135,20	14,01
A_2CH_4	17	136,19	16,31
A_2CH_5	17	130,36	18,67
Logical Relations variables			
A_LRS_2	17	31,58	9,28
A_LRS_3	17	33,42	8,02
A_LRS_4	17	32,73	8,69
A_LRS_5	17	33,69	8,67
Matching to Sample variables			
A_M2S_2	17	46,98	16,67
A_M2S_3	17	45,59	18,99
A_M2S_4	17	43,35	19,42
A_M2S_5	17	46,54	18,31
Pursuit Tracking variables			
A_PRT_2	17	8,31	2,12
A_PRT_3	17	8,41	2,41
A_PRT_4	17	7,98	1,46
A_PRT_5	17	7,91	1,70

Variables	N	Mean	Standard Deviation
Mathematical Processing variables			
A_MTH_2	17	25,48	7,24
A_MTH_3	17	27,60	6,48
A_MTH_4	17	27,34	8,34
A_MTH_5	17	27,91	9,46
Manikin variables			
A_MKV_2	17	53,89	17,81
A_MKV_3	17	52,97	15,67
A_MKV_4	17	55,05	15,17
A_MKV_5	17	57,17	18,20
Switching variables			
A_SWW_2	17	34,59	8,90
A_SWW_3	17	35,02	8,55
A_SWW_4	17	35,30	9,42
A_SWW_5	17	39,44	10,63

Repeated measures MANOVA of ANAM testing

A one-way repeated measures multivariate analysis of variance (MANOVA) was performed to investigate differences of a composite dependent variable, cognitive performance, as measured by the eight dependent variables (i.e. the ANAM subtests of Running memory continuous performance test, 2-choice reaction time test, Logical relations test, Matching to sample test, Mathematical processing test, Manikin test, and Switching test) across four test occasions (Table 10). The independent variable was oxygen level with two conditions: 21% O_2 (i.e. normal room air) during baseline testing and the nitrogen-balanced breathing gas mixture with 15% O_2 during the experimental condition at three occasions[11]. Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance and covariance[12], and multicollinearity, with no serious violations noted. Table 10 presents descriptive statistics for the composite dependent variable (cognitive performance) across the four occasions.

Table 10. *Descriptive statistics for the four ANAM test occasions compared with repeated measures MANOVA.*

Occasion	N	Mean (MANOVA composite)	Standard Deviation
Occasion 2 (Baseline)	17	54.94	2.08
Occasion 3 (Exposure 1)	17	55.37	1.99
Occasion 4 (Exposure 2)	17	55.20	2.14
Occasion 5 (Exposure 3)	17	56.54	2.39

[11] In order to be able to draw conclusions that support or reject the stated hypotheses, the comparison of experimental interest is the comparison of results from the baseline and the three experimental exposures to 15% oxygen. The results from training and post-test occasions are separately presented under the analysis of practice effects in Appendix 7.7.

[12] Due to the within-subjects design, the homogeneity of variance between occasions with 15% and 21% oxygen was evaluated on a transposed dataset, where the repeated measures design was ignored. Box's test of equality of covariance matrices and Levene's test of equality of error variance indicated no serious violations, hence preliminary assumption testing allowed the MANOVA to be conducted.

Figure 19 presents a graph of the mean results for each of the eight subtests and the MANOVA composite dependent variable across the four compared test occasions.

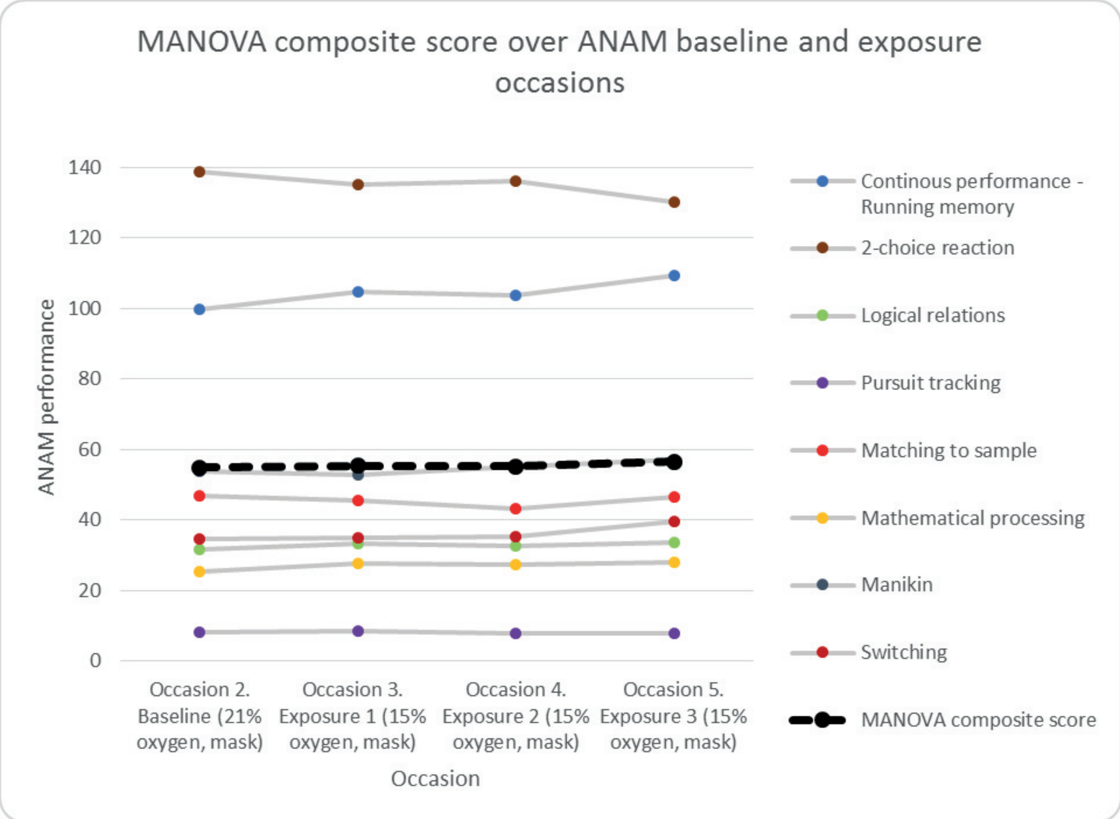

Figure 19. The mean results from the eight ANAM subtest over four occasions: baseline (#2) and the three occasions in experimental condition (#4-6) (graphically suppressed in gray) with the MANOVA composite dependent variable (graphically highlighted with the thick black dotted line).

There were no statistically significant differences observed for test occasion on the composite dependent variable (cognitive performance): F (3, 14) = .983, p= .429; Wilks' Lambda= .826; partial eta squared= .174.

6.3.7. Fatigue ratings

Descriptive data fatigue ratings

In Table 11 and Figure 20 below the mean subjective rating of fatigue on the Samn-Perelli scale are presented.

Table 11. *Mean fatigue ratings for the ten rating occasions.*

Occasion	0_2 level	Mask	Mean	SD	Max	Median	Range
1	21%	No mask	2.1	0.8	4	2	3
2	15%	Mask	1.7	0.8	3	2	2
3	15%	Mask	2.2	1.0	4	2	3
4	15%	Mask	2.0	1.1	4	2	3

Occasion	0_2 level	Mask	Mean	SD	Max	Median	Range
5	15%	Mask	1.9	0.8	3	2	2
6	15%	Mask	2.0	1.1	4	2	3
7	15%	Mask	2.5	1.2	4	2.5	3
8	15%	Mask	2.4	1.3	5	2	4
9	15%	Mask	2.2	1.0	4	2	3
10	21%	No mask	2.4	1.2	5	2.5	4

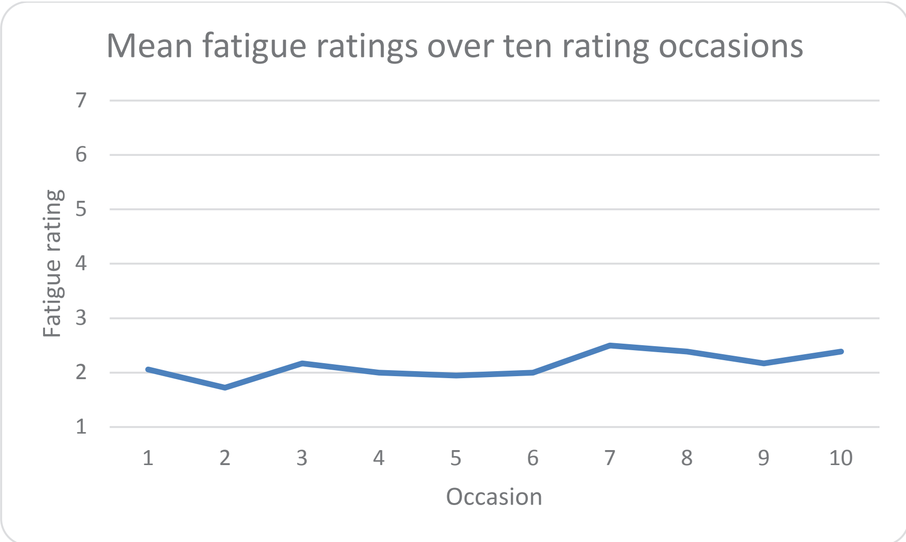

Figure 20. Fatigue ratings (experimental conditions for the rating occasions can be found in Table 11).

6.3.8. Discomfort ratings

Descriptive data discomfort ratings

In Table 12 and Figure 21 below the means of the subjective discomfort ratings are presented.

Table 12. *Mean discomfort ratings over ten rating occasions.*

Occasion	O_2 level	Mask	Mean	SD	Max	Median	Range
1	21%	No mask	1.3	0.0	1	1	0
2	15%	Mask	1.2	0.8	4	1	3
3	15%	Mask	1.2	0.4	2	1	1
4	15%	Mask	1.1	0.4	2	1	1
5	15%	Mask	1.3	0.2	2	1	1
6	15%	Mask	1.1	0.8	4	1	3
7	15%	Mask	1.1	0.3	2	1	1
8	15%	Mask	1.2	0.2	2	1	1
9	15%	Mask	1.2	0.5	3	1	2
10	21%	No mask	1.2	0.7	4	1	3

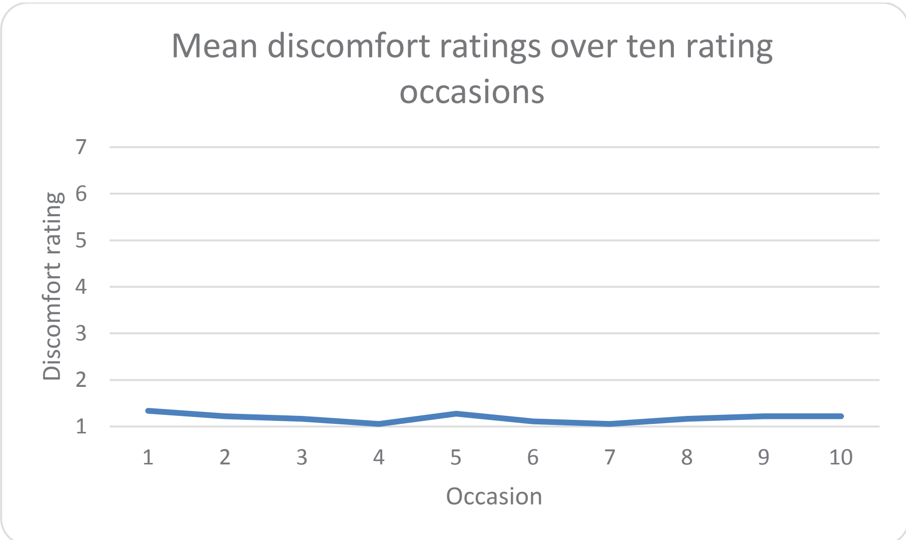

Figure 21. Discomfort ratings (experimental conditions for the rating occasions can be found in Table 12).

6.3.9. Hypoxic symptoms ratings

Descriptive data hypoxic symptoms ratings

In
Table 13, the subjective ratings of hypoxic symptoms are summarised.

Table 13. *Hypoxic symptoms ratings for the 14 listed symptoms.*

Symptom	Max	Mean	SD
1 = do not perceive at all			
2 = perceive something			
3 = perceive clearly			
Un-normal sensation of pricking, tickling or tingling in the skin	2	1.1	0.2
Increased rate and/or depth of breathing	2	1.4	0.5
Headache	3	1.4	0.6
Drowsiness	2	1.4	0.5
Heart rate that exceeds the normal range	1	1.0	0.0
Light-headedness	2	1.2	0.4
Impaired muscle coordination	1	1.0	0.0
Impaired vision	2	1.1	0.2
A feeling of “non-presence”	2	1.1	0.3
Changes in light sensitivity/perceived light intensity	2	1.1	0.2
Memory impairments	2	1.1	0.3
Concentration impairments	2	1.4	0.5
Easily distracted	2	1.2	0.4
Nausea	2	1.1	0.2

7. Discussion

7.1. Empirical observations

The analysis of the K-D test completion times in Section 6.3.5 clearly indicate that the experimental condition, i.e. the hypoxic exposure of 15% O_2, did not result in cognitive performance decrements, as measured by the K-D test. The MANOVA that was conducted on the ANAM results in Section 6.3.6 consistently points towards the same conclusion based on the comparison of the composite dependent variable of cognitive performance (composed by the eight cognitive subtest variables per occasion) across baseline and experimental exposure test occasions.

The control for fatigue, discomfort, and hypoxic symptoms through subjective ratings did not exhibit any results worth commenting, other than that the participants did not experience fatigue during the experiment. They were not disturbed by anything in the facility, including the breathing mask.

The MANOVA of the ANAM results, and the ANOVA from the K-D test, suggest that the null hypothesis (H0), based on the experimental conditions of the empirical study, should be retained. In other words, no negative effects should be expected to occur on cognitive functions due to hypoxic exposure to 15% O_2. However, it should be noted that there are related factors, for example health screening and personal health as well as physical activity while under hypoxic exposure, which may induce interaction effects, which may result in a negative impact on cognitive performance. This is further discussed in Section 7.3.

7.2. Methodological considerations

The overarching methodological conclusion was that the research design was appropriate and functional. The measures, the administration of the measures, the breathing masks, as well as the facility and procedures worked with efficiency and according to plan.

7.2.1. Practice effects

Practice effects may induce confounding factors in psychological studies, and hence an analysis of practice effects of King-Devick and ANAM testing has been conducted. Despite the automatic embedded variations of ANAM stimuli, i.e. the pseudo-randomization procedure that permits creation of near-limitless alternate versions of stimuli sets, it cannot be neglected that participants may develop a strategy for test execution during the repeated measurements. Appendix 9.7 presents practice effect analyses for King-Devick and ANAM test results.

The conclusion from the analysis of practice effects is that there are no effects imposing risks to the empirical or practical conclusions of the study. The practice effect analysis of King-Devick test results show no implications for the statistical hypothesis testing. For ANAM, six tests show no significant results indicating a risk for confounding while two tests have some scattered effects of “late” occasion showing higher performance (exposure 3 and post-test). However, any risks for confounding were mitigated since statistical hypothesis testing based on ANAM results was focused to baseline and the three experimental exposure occasions, and further by the choice of MANOVA with composite dependent variables (composed by the eight ANAM tests per occasion) for comparison of cognitive performance across the four occasions.

7.2.2. Mask effects

During the planning phase of the experiment, efforts were invested into testing a breathing mask that was acceptable for long-time use by participants previously unaccustomed to breathing masks. This effort proved fruitful, and the discomfort ratings indicate that the mask was not perceived as disturbing. Since the mask was worn during the collection of baseline data, any effects of the mask would regardless have been balanced across baseline and experimental testing occasions. No leaks into the masks, with risks for increased oxygen by room air during the experimental condition, were observed.

7.2.3. Fatigue effects

The rather low fatigue ratings indicate that the participants reported indicate that they did not experience fatigue during participation. The very weak correlation with the K-D test completion times also indicates that fatigue did not interfere with performance. As noted above the third experimental exposure was 45 minutes as compared to the first two 2-hours exposures. This was done order to reduce the risk of fatigue confounding results as training and post-testing also was required. This shorter third exposure is not deemed to affect the conclusions from the experiment. There are no experimental or logical indications that any effects in the two additional K-D tests that would have been conducted under a full 2-hours third exposure would be due to hypoxia.

7.3. Opportunities for further analysis and research

7.3.1. Gas mixes

The mixture of different gases is not necessarily as rapid and straightforward as might be expected. In closed systems with oxygen reduction in physically heterogeneous spaces, a controlled mixture of oxygen and nitrogen cannot be taken for granted at all places and at all times. Experiences (personal communication with Åke Larson[13], research engineer in the studies reported by Gustafsson et al., 1997) indicate that gas pockets with quite deviating gas mixtures may appear in closed heterogeneous spaces. Depending on the layout of the rooms as well as equipment and furniture (e.g. cabinets), pockets with lower oxygen levels might evolve at worst exposing operators to more serious hypoxic conditions than expected. Hence, effects of hypoxia at lower levels than 15% O_2 may have to be considered. For the same reasons, hyperventilation as an effect of local extremes of carbon dioxide (CO_2) may also be worth considering.

[13] Personal communication Åke Larsson, March 2014.

7.3.2. Effects of air humidity

During normobaric hypoxic exposure, air humidity is a factor worth considering when calculating the oxygen level in the reduced oxygen gas mix that is used. In short, the available (inspired) oxygen is higher in dry gas than in humid gas. The effect is that if the oxygen level of a certain altitude is to be simulated under normobaric conditions (i.e. sea level) or another altitude level, the oxygen concentration may need to be compensated to correspond correctly to that altitude, depending on whether the gas mixture is dry or humid.

7.3.3. Visual perception effects

As described in the literature study, e.g. Balldin et al. (2007); Hovis et al. (2013), decrements to light sensitivity of the dark-adapted eye is one of the first perceptual-cognitive areas that are affected by hypoxia. Minor decrements in visual perception of the dark-adapted eye have been observed at the oxygen levels that were studied in this experiment. Based on the normal light conditions at a nuclear power plant, no test of visual perception was included in the experiment. However, crisis management and emergency situations, such minor decrements could, depending on power plant design and emergency equipment factors, be worthwhile to consider.

7.3.4. Interaction effects

If any decrements on cognitive performance would at the oxygen level studied here, they would most plausibly appear due to interaction effects with other factors, rather than as an isolated hypoxic effect. As reported in the scientific literature (e.g. Temme et al., 2013), the effects of a previous concussion may interact with hypoxic symptoms and reactions. Other factors that may have an effect are haemoglobin level, smoking habits, overall health/fitness as well as some diseases, medicines, and drugs, which could lead to situations where decrements on cognitive performance increase as an effect of interaction.

The interaction effects between hypoxia and physical effort have been studied during a number of research efforts (e.g. Bartholomew et al., 1999; Gustafsson et al., 1997, Ando et al, 2013). In the exempt permit to FKA (Swedish Work Environment Authority, 2011), it is prescribed that oxygen levels must be increased to 21% O_2 (i.e. normal room air) in the environment if more demanding physical tasks are to be undertaken. Due to this prescription, interaction effects from physical effort with hypoxia were not studied in the experiment.

7.3.5. Risk taking behaviour

The reported experiment, in line with previous similar research, focused on measuring basic cognitive performance, as these functions are the foundation for higher-order functions, such as decision-making (i.e. more complex decisions than e.g. the logical reasoning tasks used in ANAM). Pighin el al. (2012; 2014) suggest that higher-order cognitive functions such as risk taking behaviour may be affected by hypoxia, and call for more studies on hypoxic effects on higher-order cognition. The current experiment could not encompass this due to budget constraints, but a study of how risk taking behaviour, possibly in a two person team context, is affected by hypoxia may be a relevant follow-on project. The design of such a study should also include an experiment environment and work tasks that to a higher extent resemble the real work situation (e.g. participants should be able to move around, without breathing masks, while encountering realistic risk related work tasks).

7.4. Practical implications

The compiled conclusion from the study, with literature review and experiment considered, is that no cognitive effects should be expected given the studied conditions, i.e. 15% O_2 under normobaric conditions during a work schedule of three times two hours[14] with 15 min and 30 min breaks between exposures. There is no evidence to consider the mild, acute hypoxia of 15% O_2 under this exposure schedule to impose any cognitive decrements, as an isolated effect of hypoxia (with the exception of decrements to light sensitivity of the dark-adapted eye). However, it should once again be noted that interaction effects with other phenomena/conditions such as physical strain, smoking, concussion and other medical conditions, have been found by other researchers.

[14] Despite the third exposure being 45 minutes, as described under 6.2.3

8. References

Digital object identifiers (doi) have been included when available.

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9. Appendices

9.1. Appendix A: Corresponding altitudes in ft/m and oxygen levels

Feet to meter conversion: altitude in m = altitude in ft / 3.2808
Meter to feet conversion: altitude in ft = altitude in m x 3.2808

Altitude (ft)	Altitude (m)	Oxygen (%)
0	0	20.9
1,000	305	20.1
2,000	610	19.4
3,000	914	18.6
4,000	1,219	17.9
5,000	1,524	17.2
6,000	1,829	16.6
7,000	2,134	16.0
8,000	2,438	15.4
9,000	2,743	14.8
10,000	3,048	14.2
11,000	3,353	13.7
12,000	3,658	13.2
13,000	3,962	12.7
14,000	4,267	12.2
15,000	4,572	11.7
16,000	4,877	11.3
17,000	5,182	10.9
18,000	5,486	10.5
19,000	5,791	10.1
20,000	6,096	9.7

9.2. Appendix B: Summary of publications on normobaric hypoxia

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Ando et al. (2013)	21%, 18%, 15%	Mild	N	Psychomotor Physiological	12	Hypoxia did not affect reaction time or response accuracy.
Bonnon et al. (1995)	4,383 m	Moderate	N	Psychomotor Emotional	6+6	Evidence for use of certain defence mechanisms, e.g. self-concern, was found 8-20 hr after ascent to altitude with recovery after 48-60 hr.
Degia et al. (2003)	2,500 m	Mild	N	Cognitive Psychomotor Perceptual	8	No significant differences between hypoxic vs normoxic test conditions were detected.
Fowler et al. (1985)	16% (8.000 ft, 2,438 m) to 11% (17.000 ft, 5181 m)	Moderate	N	Cognitive Psychomotor	Experiment 1: 32 Experiment 2: 20	No impairment of learning found, up to 12,000 ft.
Gustafsson et al. (1997); Gustafsson et al. (1998); Linde et al. (1997)	15%, 14%, 13%	Mild	N	Cognitive Psychomotor Emotional Perceptual	22	Exposure to normobaric hypoxia with a 14% and 15% O_2 concentration for several days did not affect psychomotor or cognitive performance significantly. The same conclusion was valid also for exposure to 13% O_2 for 24 hr with no significant decrements in performance. However, for some participants the subjective discomfort ratings indicated symptoms of acute mountain sickness.

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Knight et al. (1990)	21%, 13%, 17%	Mild	N	Cognitive Emotional Physiological	13	Normobaric 17 % O_2 level was acceptable, but normobaric 13 % O_2 level produced short-term decrements in cognitive functioning and mood with moderate symptoms of acute mountain sickness for some individuals.
Hewett et al. (2009)	14,000 ft, 12,000 ft, 10,000 ft, 8,000 ft, sea level	Moderate	N	Cognitive Physiological	50	No significant cognitive deficiencies for exposure times of 45 min at studied oxygen levels.
Lawler et al. (1988)	21%, 14%	Mild	N	Physiological	7+6	Highly trained endurance athletes suffer more severe physiological impairments during acute exposure to hypoxia than untrained individuals.
Legg et al. (2014)	2,438 m, sea level	Mild	N	Cognitive (decision-making)	25	Results indicate that mild hypoxia impair working memory and complex logical reasoning involving difficult conflicts.
Markou et al. (2001)	90% oxygen blood saturation	Moderate	N	Cognitive Physiological	15+15	Hypoxia did not affect performance of memory scanning tasks.
Nesthus et al. (1997)	12,500 ft, 8,000 ft, 5,000 ft, sea level	Moderate	N	Cognitive Physiological	9+9	Smokers experience a detriments of peripheral vision and ability to visually monitor several tasks simultaneously.

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Noble et al. (1993)	80% oxygen blood saturation	Moderate	N	Cognitive Psychomotor	-	Mean oxygen saturation of 78% caused only minor changes in cognitive functions.
Piehl Aulin et al. (1998)	2,700 m, 2,000 m, sea level	Mild	N	Physiological Emotional	6+9+5	No changes in oxygen uptake, blood pressure and mood states. Intermittent normobaric hypoxia for 10 days resulted in a significant stimulation of production of red blood cells.
Pighin et al. (2012)	21%, 14%	Mild	N	Cognition (decision making) Psychomotor	30	For choices involving potential gambling losses, participants were more risk seeking in environment with reduced oxygen. For those involving gains, no difference was found.
Pighin et al. (2014)	21%, 14%	Mild	N	Cognition (decision making) Psychomotor	26	Mild hypoxia decreased loss aversion.
Roach et al. (1996)	4,564 m	Moderate	N	Physiological	9	Hypobaric hypoxic conditions induced acute mountain sickness (AMS) to a greater extent than both normobaric hypoxia and normoxic hypobaria, although normobaric hypoxia induced some AMS.

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Sausen et al. (2001)	21%, 7.85%, 7%, 6.20%	Severe	N	Physiological	12	Results consistent with those expected from hypoxic states and interpreted as supporting the validity of the reduced oxygen breathing paradigm for hypoxia training.
Temme et al. (2013)	14,000 ft, 12,000 ft, 8,000 ft, sea level	Moderate	N	Cognitive	36+36	Although there were no significant differences in cognitive performance at sea level, with increased altitude, the participants with a concussion history were significantly more affected by hypoxia than that of the control group.
Westerman (2004)	25,000 ft	Severe	N	Cognitive Physiological	452	Conclusion was that the use of reduced oxygen breathing to simulate 25,000 ft altitude is a safe, convenient and cost effective way to demonstrate the effects of hypoxia.

9.3. Appendix C: Summary of publications on hypobaric hypoxia

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Balldin et al. (2007)	10,000 ft	Mild	H	Cognitive Perceptual Physiological	30	No significant negative impact on cognitive function during 12 hr exposure. Minor negative effects visual performance under starlight conditions.
Cable (2003)	Up to 19,000 ft	Moderate	H	Survey, literature review or textbook	-	Hypoxia incidents most commonly occur at altitudes less than 19,000 ft.
Hovis et al. (2013)	3,789 m, 394 m	Mild	H	Perceptual	16	Small perceptual effects, i.e. increases in the red-green threshold.
Malle et al. (2013)	10,000 m, sea level	Severe	H	Cognitive	28+29	Working memory is severely impaired by acute hypobaric hypoxia.
Paul and Fraser (1994)	3,660 m, 3,050 m, 2,440 m, 1,525 m	Mild	H	Cognitive Psychomotor	144	Results indicate that the ability to learn new tasks not is impaired by mild hypoxia up to 3,660 m.

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Pavlicek et al. (2005)	4,500 m, 3,000 m	Moderate	H	Cognitive Emotional	21	No significant changes in higher cognitive and emotional function tests between hypoxic conditions.
Shukitt-Hale (1998)	4,700 m, 4,200 m, 500 m	Moderate	H	Cognitive Psychomotor Emotional Perceptual	23	Exposure to altitude significantly affected symptoms, moods, and performance. Adverse changes increased with higher altitudes. Only some measures were affected at 4,200 m, all were affected at 4,700 m, and effects were usually with a longer duration.

9.4. Appendix D: Summary of publications on both normobaric and hypobaric hypoxia

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Denison et al. (1966)	8,000 ft, 5,000 ft	Mild	H/N	Psychomotor Physiological	Experiment 1: 8 Experiment 2: 28	Mild hypoxia affects performance of a novel task.
Evetts et al. (2005)	21%, 10,3%, 6,9%	Severe	H/N	Psychomotor Physiological	11	For the purposes of hypoxia training, inducing hypoxia using low concentrations of oxygen at ground level and at 10,000 ft produces virtually the same physiological and performance responses and identical symptoms as breathing air at 25,000 ft.
Roach et al. (1996)	4,564 m	Moderate	H/N	Physiological	9	Hypobaric hypoxic conditions induced acute mountain sickness (AMS) to a greater extent than does either normobaric hypoxia or normoxic hypobaria, although normobaric hypoxia induced some AMS.
Vacchiano et al. (2004)	25,000 ft	Severe	H/N	Cognitive Physiological	70	Effects of hypoxia were the same regardless of normobaric or hypobaric conditions.

9.5. Appendix E: Summary of publications with unclear hypoxic conditions

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
Bartholomew et al. (1999)	15,000 ft, 12,500 ft	Moderate	-	Cognitive Perceptual	72	No effects of altitude were found in performance on a vigilance task. For read-backs of information during high memory load, significant deficits in recall were observed at 12,500 ft and 15,000 ft, whereas no effect of altitude was observed on recall of read-backs with low memory loads.
Rice et al. (2005)	15,000 ft, 12,000 ft, 10,000 ft	Moderate	-	Cognitive Psychomotor	60	A statistically significant finding was found in accuracy during a vigilance subtest for 15,000 ft. Analysis of reaction time and accuracy indicated no significant differences.
Watson et al. (2000)	3,700 m, 2,400 m, 1,200 m, sea level	Mild	-	Perceptual	-	Sensitivity for frequencies up to 16 kHz is unaffected by hypoxia.
Woorons et al. (2007)	18.7%, 17.3%, 15.5%, 13%, 11.7%	Severe	-	Physiological	7+7	Results indicate that moderate

Author(s) (Year)	Altitude (ft or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures used in study	Number of participants (exposed + control group if two numbers)	Major Results
						exercise under hypoxia, contrary to normoxic conditions, can lead to a greater arterial desaturation in trained men compared with untrained men.

9.6. Appendix F: Summary of literature reviews, surveys, and textbook chapters

Author(s) (Year)	Altitude (ft. or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures	Number of participants (exposed + control group if two numbers)	Major Results
Angerer & Nowak (2003)	15%, 13%	Mild	-	Survey, literature review or textbook	-	Working in environments oxygen concentrations down to a minimum of 13% O_2 and normal barometric pressure do not impose a health hazard for healthy persons although evidence is limited, regarding workers performing physical tasks or having various diseases.
Burtscher et al. (2012)	Up to 3,000 m (14.5% O_2)	Mild	-	Survey, literature review or textbook	-	Physical activity and unusual environmental conditions may increase effects of hypoxia. Large inter-individual variations of responses to hypoxia have to be expected, especially in persons with pre-existing diseases.
Cable (2003)	Up to 19,000 ft	Moderate	H	Survey, literature review or textbook	-	Hypoxia incidents most commonly occur at altitudes less than 19.000 ft.

Author(s) (Year)	Altitude (ft. or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures	Number of participants (exposed + control group if two numbers)	Major Results
Deussing et al (2010)	-	-	H/N	Survey, literature review or textbook	566	Results indicate that only 21% of hypoxia events were reported in aviation hazard reports. 57% of hypoxia events occurred with the oxygen mask off. In-flight, mask-on hypoxia has a similar overall symptom profile to reduced oxygen training, but significant differences exist between five individual symptoms**.**
Ernsting et al. (1988)	-	-	-	Survey, literature review or textbook	-	A seminal work that provides aviation hypoxia.
Fulco & Cymerman (1988)	-		-	Survey, literature review or textbook	-	Describes visual impairment among other physiological effects of hypoxia.
Küpper et al. (2009)	-	Mild	-	Survey, literature review or textbook	-	Provides recommendations concerning normal work in hypoxic environments.
Paul & Gray (2002)	-	-	-	Survey, literature review or textbook	-	Exposure time to cabin altitudes of 8,000 to 10,000 ft should be limited to 4 hr. If operational requirements dictate longer exposure, supplementary oxygen should be provided.

Author(s) (Year)	Altitude (ft. or m)/ O_2 concentration (%)	Highest Hypoxic exposure (mild, moderate, severe)	Method (hypobaric [H]/normobaric [N])	Types of measures	Number of participants (exposed + control group if two numbers)	Major Results
Petrassi et al. (2011), Petrassi et al. (2012)	15,000 ft to 8,000 ft	Moderate	-	Survey, literature review or textbook	-	Systematic literature reviews of research on acute hypoxic hypoxia within 8,000 to 15,000 ft.
Smith (2005)	-	Severe	-	Survey, literature review or textbook	53	Aircrew experienced potentially operationally significant symptoms at a mean altitude of 8,426 ft.

9.7. Appendix G: Analyses of practice effects

In this appendix, a number of ancillary analyses are presented to shed light on practice effects for King-Devick and ANAM testing respectively. This means that all test occasions: training, baseline, experimental test occasions, and post-testing are presented and analysed with regard to practice effects. For King-Devick testing, this means that the four training occasions and the post-test occasions are presented together with the baseline and the ten experimental occasions. For ANAM, the training and the post-test occasions are presented in addition to the baseline occasion and the three experimental occasions.

Practice effect analysis of King-Devick test results

Table 14 and Figure 22 presents the K-D test results across the total of 16 test occasions, i.e. with the four training occasions and the post-test occasion included, to visualise how performance on the K-D test stabilizes after the four training occasions (in accordance with the guidelines from the provider), with the largest performance change occurring between the first and second test occasion.

Table 14. *Descriptive statistics for King-Devick test performance scores for all test occasions, incl. training occasions and the post-test occasion.*

Occasion	N	Mean	Standard Deviation
KD1_time (Training occasion 1))	18	57,27	13,79
KD2_time (Training occasion 2)	18	48,11	7,38
KD3_time (Training occasion 3)	18	45,40	5,32
KD4_time (Training occasion 4)	18	43,30	4,74
KD5_time (Baseline)	18	46,20	6,18
KD6_time (Exposure 1, 3 min)	18	45,63	6,63
KD7_time (Exposure 1, 10 min)	18	44,03	6,33
KD8_time (Exposure 1, 60 min)	18	45,08	7,11
KD9_time (Exposure 1, 110 min)	18	44,46	6,97
KD10_time (Exposure 2, 3 min)	18	44,67	6,09
KD11_time (Exposure 2, 10 min)	18	43,98	5,81
KD12_time (Exposure 2, 60 min)	18	44,50	5,98
KD13_time (Exposure 2, 110 min)	18	44,97	6,91
KD14_time (Exposure 3, 3 min)	18	43,38	6,05
KD15_time (Exposure 3, 10 min)	18	42,76	6,46
KD16_time (Post-test)	18	43,88	7,10

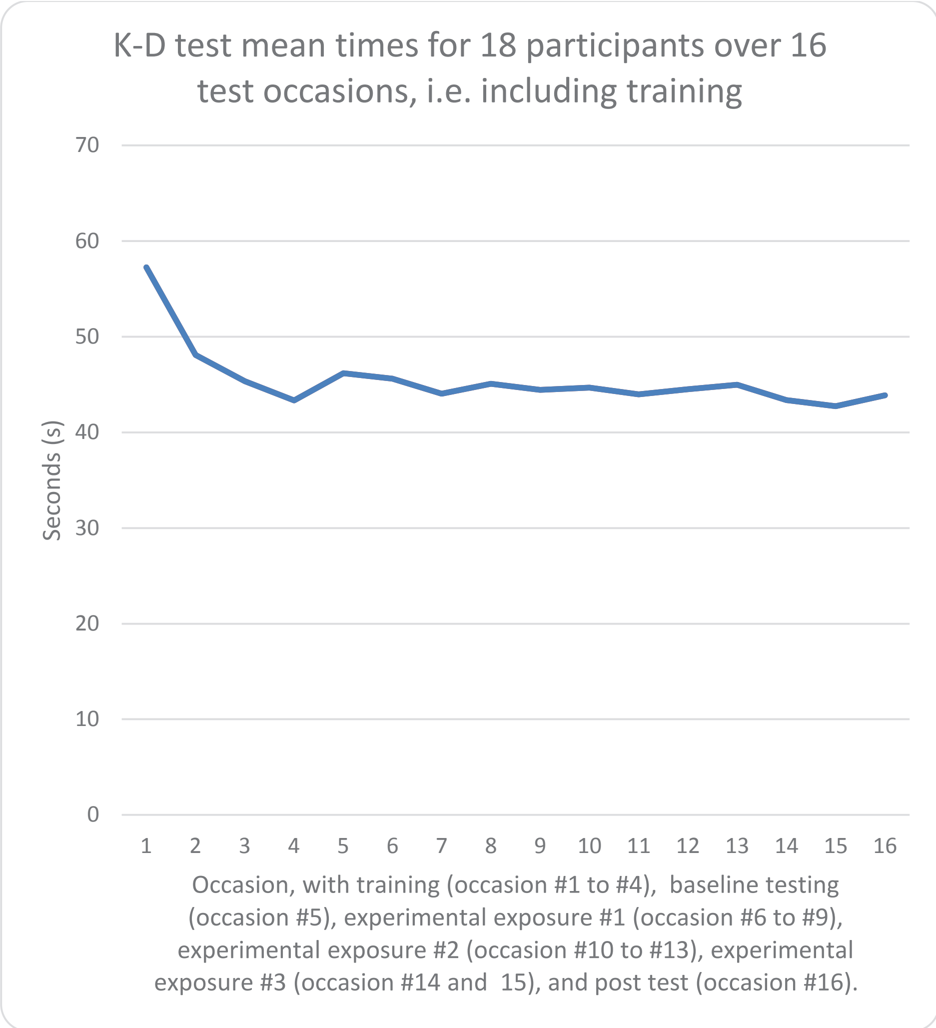

Figure 22. King-Devick test results including training occasions and the post-test occasion.

A one-way repeated measures analysis of variance (ANOVA) was conducted to compare scores on the sixteen K-D test occasions. However, Mauchly's test of sphericity indicated that the sphericity assumption had been violated, χ^2 (119) = 278.810, $p < .05$, and therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .147$). The results showed that there was a significant effect of occasion, $F(2.206, 37.500) = 13.613$, $p < .05$.

Post-hoc analysis of Table 14 and the pairwise comparison output from the statistical tool SPSS showed that statistically significant differences were observed between the first training occasion (KD1_time) and several of the other test occasions (KD4_time, KD5_time, KD7_time, KD8_time, KD10_time, KD11_time, KD14_time, KD15_time, KD16_time). No other significant differences were observed.

The conclusion from the King-Devick practice effects analysis is that no effects were observed, beyond the initial and intended effect of training, and there are no implications of practice effects for the statistical hypothesis testing based on the King-Devick test results.

Practice effect analysis of ANAM test results

A series of one-way repeated measures ANOVA's (Analysis of Variance) were conducted to shed light on any practice effects throughout the repeated ANAM testing. Figure 23 presents a graph over the mean results for each ANAM subtest across the six occasions.

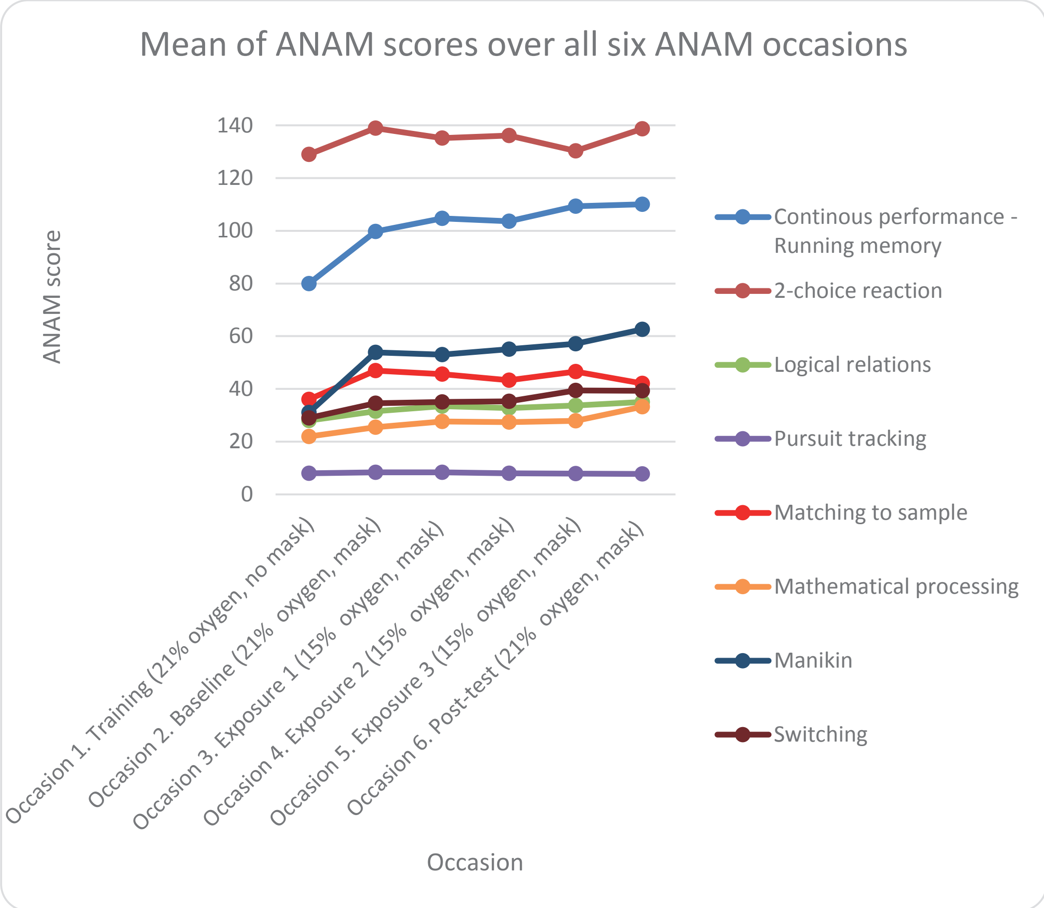

Figure 23. The mean results from the eight ANAM subtest over all six occasions, i.e. including training.

ANAM Running memory – Continuous Performance, A_CPT

A one-way repeated measures ANOVA was conducted to compare results on the Running Memory – Continuous Performance (CPT) subtest of ANAM across the six test occasions. Descriptive data are presented in Table 15. However, Mauchly's test of sphericity indicated that the sphericity assumption had been violated, χ^2 (14) = 34.915, $p < .05$, and therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .574$). The results showed that there was a significant effect of occasion, $F(2.871, 45.939) = 35.878$, $p < .05$.

Table 15. *Descriptive statistics for ANAM Running Memory – Continuous Performance scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	80.31	18.53
Occasion 2 (Baseline)	17	99.72	19.61
Occasion 3 (Exposure 1)	17	104.73	20.73
Occasion 4 (Exposure 2)	17	103.66	21.09

Occasion	N	Mean	Standard Deviation
Occasion 5 (Exposure 3)	17	109.27	18.16
Occasion 6 (Post-test)	17	110.10	18.29

Post-hoc analysis of Table 15 and of the pairwise comparisons output from the statistical tool SPSS showed that the statistically significant differences were observed between the training occasion and all other occasions, i.e. performance during the training session was significantly lower than during all other occasions. Furthermore, baseline performance was significantly lower than performance at exposure 3 and post-test, and performance at exposure 1 was significantly lower than post-test performance.

ANAM 2-choice reaction, A_2CH

A one-way repeated measures ANOVA was conducted to compare results on the 2-choice reaction (2CH) subtest of ANAM across the six test occasions. Descriptive data are presented in Table 16. Mauchly's test of sphericity indicated that the sphericity assumption had been violated, χ^2 (14) = 41.880, p < .05, and therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = .409). The results showed that there was no significant effect of occasion, F(2.044, 32.707) = 1.837, p < .175, and hence no significant differences were observed for this test across the six test occasions.

Table 16. *Descriptive statistics for ANAM 2-choice reaction scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	129.54	26.91
Occasion 2 (Baseline)	17	138.92	18.15
Occasion 3 (Exposure 1)	17	135.20	14.01
Occasion 4 (Exposure 2)	17	136.19	16.32
Occasion 5 (Exposure 3)	17	130.37	18.67
Occasion 6 (Post-test)	17	138.75	16.59

ANAM Logical Relations, A_LRS

A one-way repeated measures ANOVA was conducted to compare results on the Logical Relations (LRS) subtest of ANAM which the participants completed at six occasions (Training, Baseline, Exposure 1, Exposure 2, Exposure 3, Post-test). Descriptive data are presented in Table 17. However, Mauchly's test of sphericity indicated that the sphericity assumption had been violated, χ^2 (14) = 24.450, p < .05, and therefore the degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε = .871). The results show that there was a significant effect of occasion, F(4.353, 69.645) = 6.837, p < .05.

Table 17. *Descriptive statistics for ANAM Logical Relations scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	28.01	7.39
Occasion 2 (Baseline)	17	31.59	9.29
Occasion 3 (Exposure 1)	17	33.42	8.03

Occasion	N	Mean	Standard Deviation
Occasion 4 (Exposure 2)	17	32.74	8.69
Occasion 5 (Exposure 3)	17	33.70	8.68
Occasion 6 (Post-test)	17	35.00	8.27

Post-hoc analysis of Table 17 and the pairwise comparison output from the statistical tool SPSS showed that statistically significant differences were observed between the training occasion as compared to exposure 1, exposure 3, and post-test, i.e. that performance during training was significantly lower than during the aforementioned occasions.

ANAM Pursuit Tracking, A_PRT

A one-way repeated measures ANOVA was conducted to compare results on the Pursuit Tracking (PRT) subtest of ANAM across the six test occasions. The means and standard deviations are presented in Table 18. There was no significant effect of occasion [Wilks' Lambda = .665, $F(5, 12) = 1.207$, $p = .363$, multivariate partial eta squared = .335], meaning that no significant differences were observed for this test across the six test occasions.

Table 18. *Descriptive statistics for ANAM Pursuit Tracking scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	8.35	1.76
Occasion 2 (Baseline)	17	8.31	2.12
Occasion 3 (Exposure 1)	17	8.41	2.42
Occasion 4 (Exposure 2)	17	7.99	1.47
Occasion 5 (Exposure 3)	17	7.91	1.71
Occasion 6 (Post-test)	17	7.73	176

ANAM Matching to Sample, A_M2S

A one-way repeated measures ANOVA was conducted to compare results on the Matching to Sample (M2S) subtest of ANAM across the six test occasions. Descriptive data are presented in Table 19. Mauchly's test of sphericity indicated that the sphericity assumption had been violated, $\chi^2(14) = 32.228$, $p < .05$, and therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .521$). The results show that there was a significant effect of occasion, $F(2.606, 41.700) = 5.577$, $p < .05$.

Table 19. *Descriptive statistics for ANAM Matching to Sample scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	35.84	9.78
Occasion 2 (Baseline)	17	46.99	16.67
Occasion 3 (Exposure 1)	17	45.59	18.99
Occasion 4 (Exposure 2)	17	43.35	19.42
Occasion 5 (Exposure 3)	17	46.55	18.32
Occasion 6 (Post-test)	17	42.05	19.11

Post-hoc analysis of Table 19 and the pairwise comparison output from the statistical tool SPSS showed that the statistically significant difference was observed between training and baseline, i.e. performance during training was significantly lower than baseline performance.

ANAM Mathematical Processing, A_MTH

A one-way repeated measures ANOVA was conducted to compare results on the Mathematical Processing (MTH) subtest of ANAM across the six test occasions. The means and standard deviations are presented in Table 20. There was a significant effect of occasion [Wilks' Lambda = .190, $F(5, 12) = 10.233$, $p = .001$, multivariate partial eta squared = .810].

Table 20. *Descriptive statistics for ANAM Mathematical Processing scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	21.95	6.55
Occasion 2 (Baseline)	17	25.49	7.25
Occasion 3 (Exposure 1)	17	27.60	6.49
Occasion 4 (Exposure 2)	17	27.35	8.35
Occasion 5 (Exposure 3)	17	27.92	9.47
Occasion 6 (Post-test)	17	33.29	9.91

Post-hoc analysis of Table 20 and output from the statistical tool SPSS showed that that statistically significant differences were observed between the training occasion as well as the post-test occasion compared to all other occasions, i.e. performance at training was significantly lower than at all other occasions, and performance at post-testing was significantly higher than at all other occasions.

ANAM Manikin, A_MKV

A one-way repeated measures ANOVA was conducted to compare results on the Manikin (MKV) subtest of ANAM across the six test occasions. Descriptive data are presented in Table 21. However, Mauchly's test of sphericity indicated that the sphericity assumption had been violated, $\chi^2 (14) = 42.164$, $p < .05$, and therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .393$). The results show that there was a significant effect of occasion, $F(1.965, 41.439) = 34.739$, $p < .05$.

Table 21. *Descriptive statistics for ANAM Manikin scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	31.39	16.18
Occasion 2 (Baseline)	17	53.89	17.82
Occasion 3 (Exposure 1)	17	52.98	15.68
Occasion 4 (Exposure 2)	17	55.05	15.18
Occasion 5 (Exposure 3)	17	57.18	18.20
Occasion 6 (Post-test)	17	62.58	17.44

Post-hoc analysis of Table 21 and the pairwise comparison output from the statistical tool SPSS showed that the statistically significant differences were observed between training and all other occasions, i.e. that performance at training was significantly lower than performance at all other occasions.

ANAM Switching, A_SWW

A one-way repeated measures ANOVA was conducted to compare results on the Switching (SWW) subtest of ANAM across the six test occasions. The means and standard deviations are presented in Table 22. There was a significant effect of occasion [Wilks' Lambda = .814, F(5, 12) = 10.507, p = .00047, multivariate partial eta squared = .814].

Table 22. *Descriptive statistics for ANAM Switching scores for Occasion 1 to Occasion 6.*

Occasion	N	Mean	Standard Deviation
Occasion 1 (Training)	17	29.09	9.96
Occasion 2 (Baseline)	17	34.59	8.91
Occasion 3 (Exposure 1)	17	35.02	8.55
Occasion 4 (Exposure 2)	17	35.31	9.42
Occasion 5 (Exposure 3)	17	39.44	10.63
Occasion 6 (Post-test)	17	39.25	11.01

Post-hoc analysis of Table 22 and the pairwise comparison output from the statistical tool SPSS showed that the statistically significant differences were observed between the training occasions and all other occasions, as well as between exposure 3 compared to baseline, exposure 1, and exposure 2. To summarize, performance at training was significantly lower than at all other occasions, and performance during exposure 3 was significantly higher than training, baseline, exposure 1 and exposure 2.

Summary of practice effect analyses

The analysis of practice effects for King-Devick test results showed no significant practice effects beyond the initial and intended effects during initial training were observed. The performance asymptote following the fourth test occasion confirms the training recommendations from the provider of the King-Devick test. It can be concluded that there are no implications of practice effects for the statistical hypothesis testing based on the King-Devick test results.

The analysis of practice effects for the eight ANAM subtests results overall showed four patterns: a) no significant differences across the six test occasions, b) lower performance during training as compared to one or more of the other occasions, and c) higher "late-occasion" performance (exposure 2, post-test) compared to one or more of the other occasions. These are summarized by category and test below.

No significant effects. For the two tests 2-choice reaction time (2CH) and pursuit tracking (PRT) no significant differences were observed across the six test occasions.

Training performance lower than one or more other occasions. For the three tests manikin (MKV), logical relations (LRS), and matching to sample (M2S), the only statistically significant differences observed were that training performance was lower than one or more of the other test occasions. The remaining three tests for which statistically significant differences were observed, the mathematical processing test (MTH), the running memory – continuous performance test (CPT), and the switching test (SWW), significantly lower performance levels at training compared to all other occasions were observed. However these three tests also showed additional significant differences.

Higher "late-occasion" performance. For the mathematical processing test (MTH), performance at post-testing was significantly higher than at all other occasions. For the running memory - continuous performance test (CPT), baseline performance was significantly lower than performance at exposure 3 and post-test, and performance at exposure 1 was significantly lower than post-test performance. For the switching test (SWW), performance during exposure 3 was significantly higher than baseline, exposure 1 and exposure 2.

To summarize, for five of the ANAM tests (2CH, PRT, MKV, LRS, M2S), either no significant differences exists or the only difference is that training performance is lower than one or more of the other occasions. For the remaining three tests (MTH, CPT, SWW) significantly lower performance was observed at training compared to all other test occasions, however they also showed some additional effects.

For MTH, training performance is lower than at all other occasions, however in addition performance at post-testing is higher than all other occasions. Based on the descriptive data for MTH results (Table 20), it is interesting to note that there is a trend of performance increase from training (significant) to baseline to experimental exposure 1. Performance is then asymptotic across the three experimental test occasions, followed by a significant performance increase at post-testing. While there is no conclusive evidence to explain this, it may be an effect of inhibited learning due to hypoxic exposure. As mentioned in the literature review, Denison et al. 1966 reported the finding that hypoxia inhibited learning. However, no other tests show a similar pattern, and one test (SWW) show a somewhat contradictory pattern were performance at exposure 3 is significantly higher than baseline and the two other experimental occasions. CPT also show some "late" occasion effects were exposure 3 and post-test performance is significantly higher than one or more previous occasions.

The conclusion from the analysis of practice effects is that there are no effects imposing risks to the empirical or practical conclusions of the study. The practice effect analysis of King-Devick test results show no implications for the statistical hypothesis testing. For ANAM, six tests show no significant results indicating a risk for confounding while two tests have some scattered effects of "late" occasion showing higher performance (exposure 3 and post-test). However, any risks for confounding were mitigated since statistical hypothesis testing based on ANAM results was focused to baseline and the three experimental exposure occasions, and further by the choice of MANOVA with composite dependent variables (composed by the eight ANAM tests per occasion) for comparison of cognitive performance across the four occasions. Furthermore, as previously discussed in Section 6.3.6, running a series of repeated measures ANOVAs may inflate the risk of making a statistical type 1 error, i.e. by chance (rather than experimental intervention) observing an effect supporting the rejection of the null hypothesis.

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The Swedish Radiation Safety Authority has a comprehensive responsibility to ensure that society is safe from the effects of radiation. The Authority works to achieve radiation safety in a number of areas: nuclear power, medical care as well as commercial products and services. The Authority also works to achieve protection from natural radiation and to increase the level of radiation safety internationally.

The Swedish Radiation Safety Authority works proactively and preventively to protect people and the environment from the harmful effects of radiation, now and in the future. The Authority issues regulations and supervises compliance, while also supporting research, providing training and information, and issuing advice. Often, activities involving radiation require licences issued by the Authority. The Swedish Radiation Safety Authority maintains emergency preparedness around the clock with the aim of limiting the aftermath of radiation accidents and the unintentional spreading of radioactive substances. The Authority participates in international co-operation in order to promote radiation safety and finances projects aiming to raise the level of radiation safety in certain Eastern European countries.

The Authority reports to the Ministry of the Environment and has around 300 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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