



## HYPOXIA EXPOSURE AND WORKING MEMORY PERFORMANCE: A META-ANALYSIS

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**Introduction:** Working memory (WM) is an essential component of situational awareness concept as well as one of the main executive functions in cognitive psychology. Exposure to hypoxia may affect those functions and damage working memory function that could have an impact on flight safety.

**Methods:** A meta-analysis was conducted to assess the association of hypoxia effects and executive functions, particularly the WM. The studies under consideration were conducted on pilots and non-pilots performing cognitive tasks that engage working memory before and after exposure to hypoxia.

**Results:** The meta-analysis revealed a large effect size (ES) (Hedges'  $g=1.75$ ) but a distribution of particular studies presented in this paper show that larger effects are observed in studies on non-pilots, whereas small effect was observed in the pilot groups.

**Discussion:** Influence of oxygen deprivation on WM capacity was observed. Although the overall effect size was impressive indicating differences in WM capacity before and after hypoxia exposure, there is a need for discussing the results obtained in pilots and non-pilots separately and concern the role of experience and learning effects.

**Keywords:** working memory, cognitive performance, hypoxia, situational awareness, executive functions

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## INTRODUCTION

High-altitude performance demands procedural knowledge, expertise, as well as accurate and up-to-date processing. Situational awareness (SA), which, according to Endsley involves three cognitive levels: (1) continuous perception of rapidly changing situation, (2) comprehension of perceived elements in regard to previous knowledge, (3) anticipation of further events on that basis [10]. Aforementioned elements indicate a crucial role of cognitive function, especially updating and actualization of memory processes, in flight performance. Studies conducted over the last decade demonstrate the importance of SA in adverse and uncertain environments, which undoubtedly the airspace is, mainly because of the sensitivity of central nervous system to external stressors, such as decreasing air pressure in the troposphere.

By definition, hypoxia means insufficient amount of oxygen in the blood, tissues, cells of our body to maintain proper physical and mental function during the flight. Not only respiratory and circulatory systems are affected by hypoxia. Brain is the first and main organ susceptible to oxygen deprivation and hence, executive functioning.

However, little is known about WM in high-altitude flight operations. The goal of this article is to present the current state of knowledge and to outline directions for future research.

### Hypoxia as a risk factor of neuropsychological deterioration

Staying at high altitudes exposes pilots to danger of physiological abnormalities in the airspace, where barometric pressure that decreases with achieving subsequent flight levels may become a life-threatening factor. Low barometric pressure disrupts gas exchange, although the oxygen content in the atmospheric air remains unchanged (21%). Alveolar oxygen partial pressure and arterial partial pressure decrease and affect respiratory as well as circulatory system coordination. Whereas blood saturation above the sea level reaches 97-99%, under hypoxic condition can decrease to 87-94%. Although it is a non-life-threatening mild hypoxia, acute decompression can lower saturation down to 50%, which is definitely unsafe and puts the pilot in danger [5,38]. There are three ways it can influence human organism: (1) as a disturbance in oxygen metabolism - *dysoxia*, (2) as a total oxygen shortage - *anoxia*, or (3) through oxygen deficiency - *hypoxia*, which will be discussed in the paper.

Brain is the first and the main organ exposed to hypoxia. Decrease in oxygen intake causes hy-

poxia, decreasing and altering biological as well as cognitive functions. From physiological point of view the consequences of hypoxia include faster and deeper breathing, increased heart rate and changes in peripheral circulation and organ blood distribution [5].

Brain structures susceptible to hypoxia were discovered relatively early. As Virues-Ortega states [44], first studies on neuropsychological consequences of high-altitude exposure were rather anecdotal and brief than based on in-depth scientific analyses. Potential psychophysiological testing has been neglected until McFarland's research. He was the first to pay attention to the phenomenon of altitude-related neuropsychological deterioration and has published many works since 1930 that shed light on human performance under hypoxia [25,26]. It was later found that hippocampus, thalamus, cortex, amygdala, corpus striatum were the most damaged brain parts [7,46]. Later studies also confirmed that hypoxia impairs the limbic system. It was frequently observed that hypoxia affects the frontal lobes, the parts of the brain responsible for self-control and cognitive control [4,35]. Those findings inspired researchers to assume that altitude-related alterations in areas of the brain responsible for cognitive as well as emotional functioning may impact human performance and such aspects need to be tested under hypoxic conditions. Research conducted in the last decade explored a biochemical factor sensitive to high-altitude operations, such as substance P. Similar to amines, catecholamines and nitric oxide, its synthesis in the organism is modified with achieving increasingly higher flight levels. The higher flight operations, the greater increase in substance P levels is observed. It has been proven that substance P augmentation leads to mood changes, anxiety and stress [20,36]. Such states may contribute to deterioration of cognitive performance, especially WM, which is sensitive to negative arousal [33].

Hypoxia also affects climbers and alpinists above 3000 m. In the nineteenth century Mosso organized an expedition in order to study the course of acclimatization on Monte Rosa (4500m) [5]. However, there is a difference between climbers and pilots and it lies in the possibility to acclimate to harsh conditions during several days climbing. They climb, camp and descend just to ascend again in order to adapt before reaching the summit. Pilots achieve the following flight levels over a significantly shorter period of time and hence, they do not have time to adapt.

In general terms, there are several levels of hypoxia: (1) moderate (mild), equivalent to 2430-4260 m, (2) high, equivalent to 4260-5180 m, and (3) extreme (acute), corresponding to altitudes above 5200 m [23]. Little is known about the extent to which the consequences hypoxia impact executive functioning. Although brain's susceptibility to hypoxia increases from the altitude of 2430 m, the evidence suggest that staying at this altitude does not affect cognitive performance in pilots and is safe with regard to maintaining cognitive abilities. In turn, Nelson [31] states that cognitive impairment is noticeable at the altitudes from 4000 m to 5000 m. Nevertheless, there is a mandatory threshold for use of supplementary oxygen at 3000 m [23].

Pilots exposed to hypoxic and ischemic hypoxia, in order to avoid oxygen depletion, use pressurized cabins and keep the aircraft at the altitudes of 3810 - 4260 m for no longer than 30 minutes. Above this altitude and time cognitive function may become impaired, particularly in the aspect of cognitive overload and worsened executive functioning. For instance, Virues-Ortega [44] studies show that 6100 m is the altitude where neuropsychological functioning is severely impaired in aspects of verbal fluency, language, cognitive fluency, metamemory, and short-term memory. According to Petrassi [34], breathing at altitude above 6100 m is disrupting to human organism, can result in loss of consciousness and lead to death.

The level of susceptibility varies and is a matter of individual performance. As Petrassi [34] points out, some people are much more affected by hypoxia than others. There is a relatively unchanging "hypoxic signature" for every individual. This intrapersonal pattern of hypoxia can obviously vary in intensity; the order in which symptoms appear and speed of their onset may change, but it is relatively constant for an individual. However, it is rather different among subjects and it is easier for an individual to spot signs of hypoxia in others than in oneself. Observational research shows that women are more susceptible to hypoxia than men and that gender differences are in agreement with the notion that women's organisms usually demand greater amounts of oxygen on lower altitudes than men. According to Makarowski and Smolicz [23], such difference is equivalent to 610 m. Nevertheless, hypoxia used to be called a "silent killer" because of its subtle and gentle signs. Physiological as well as psychological signs and symptoms of oxygen deprivation have been in the area of scientific interest for decades. Among

them, the most often distinguished signs include dizziness, lightheadedness, paresthesia and "pins-and-needles" tingling, reduced mental agility and decreased visual acuity [43].

### **Working memory as flight safety factor**

WM is considered an interdisciplinary construct that draws attention of a wide range of psychologists and neuroscientists. As Sohn and Doane [39] noted, its role has been also demonstrated in physics, computer sciences, medicine, and language comprehension. After years of exploring WM's architecture and elaboration of a few concepts, researchers assigned it a vital role in updating information necessary for human performance.

The first and the most common model is that proposed by Baddeley, updated in 2000 [2,16,41]. Baddeley's approach assumes the existence of several elements - the main being central executive system coordinating attention and cognitive resources, engaged in decision-making and other mental operations. Apart from the central executive system there are two subordinate systems: (1) visuospatial sketchpad responsible for storage of visual data and (2) phonological (articulatory) loop responsible for auditory data storage. An episodic buffer exists between those two elements, a system responsible for temporary, episodic data integration.

WM is also a core component of executive functions model. Miyake [27] distinguished three separate EF's in factor analysis: (1) shifting, (2) inhibition of prepotent or unwanted reaction, (3) updating and monitoring. Shifting means cognitive flexibility - abandoning one task and engaging in another. Inhibition involves holding back a prepotent or unwanted reaction. And thirdly, updating and monitoring refers to working memory representations and replacing information that is no longer needed with other data. WM takes part in regulation of behavior, decision-making, directing attention and goal-oriented actions. Thus, WM is involved in cognitive control of behavior in flight performance. Neural background for those processes is assigned to prefrontal cortex (PFC), especially the frontal cortex, a structure involved in multi-tasking, susceptible to microdamages [18,29,30]. Aforementioned frontal lobe is sensitive to hypoxic conditions as well [4,35].

During flight, working memory is involved in continuous cognitive processing as well as coding, actualization, removing data that is no longer important or inhibition of those that interfere with other, more important information. According to Endsley [11,12,13], situational awareness has a rela-

tional function and the author assumes an interaction between representation of current perception and pilot's previous knowledge. Additionally, it allows comprehending current aircraft position as well as its significance and implications for future tasks. Such comprehension of actual situation and its monitoring imposes demands on WM storage and processing. Due to this fact, SA has been an object of interest since the 80's [8] and initially, its role was purely practical due to its application as a part of pilot training, especially in crew resource management [6]. Over time it has evolved as a concept bordering cognitive psychology, neuroscience and aviation studies. According to Caretta et al. study, tasks dependent on working memory performance are reliable predictors of situational awareness [8]. In those studies, verbal (phonological loop) and spatial (visuospatial sketchpad) functions of working memory were distinguished as vital to situational awareness and flight safety. In similar studies Stokes et al. [40] found that spatial working memory is predictive of decision making during flight.

## METHODS

### Identification of studies

In order to identify the consequences of hypoxia for executive functions, the author explored available reports from databases (GoogleScholar, EBSCOhost) using phrases: *executive functions*, *hypoxia*, *working memory*. The most frequent altitude levels taken into account correspond to mild to moderate (2440 - 4270 m) hypoxia. Detailed studies are presented in Tab. 1. Below are discussed selected studies, starting from the lowest altitudes (610 m) [3] to the highest (10000 m) [24]. In case of more than one hypoxic condition in a study, results are discussed in one paragraph but presented in separate rows in the table. Every study taken into consideration was approved by respective ethics committees and conformed to the standards of the Declaration of Helsinki.

1. In Bartholomew [3] study the cognitive performance during exposure to altitudes of 610 m, 2430 m and 4570 m was tested on 72 pilot students using subtests of the Wechsler Scale (Digit Span and Digit Symbol). It was observed that working memory was susceptible to impairment with respect to recalling great memory load at high altitudes equal to 3810 m and 4570 m. Such results suggest that high altitudes may affect the amount of available cognitive resources and lead to mental overload. Nonetheless, first altitude results had to

be excluded from meta-analysis because provided data hinder comparison of baseline and posttest results.

2. WM performance after exposure to hypoxia was also an object of Legg's [21] experimental study. Participants, 25 males, were experiencing normoxia as baseline and hypoxia at 2440 m for 30 and 90 minutes and subsequently were assigned multiple memory tasks (inter alia) engaging WM. Mentioned tasks required reading sentences, assessing semantic and syntactic sense of the sentence and recalling the last word of each sentence as a measure of working memory span. Study results show that after 90-minute exposure to hypoxia WM performance worsened; the mean working memory span was significantly lower than at baseline and after 30-minute exposure. Further analysis revealed moderate ES (Hedges'  $g = 0.45$ ).
3. One of the newest research studies that examined the effects of hypoxia on cognitive function was an experimental study conducted by Komiyama [19] at an altitude of 2600 m. The participants, 16 men aged 23 years on average, were asked to solve cognitive tasks such as Go/No Go (GNG) or Spatial Delayed Response (SPR) several times: before the experiment as a baseline and twice after 10 minutes of exposure to hypobaric conditions during prolonged exercise. It was observed that hypoxia exposure did not worsen the accuracy of those tasks; there was no difference in significance between baseline and after exposure to hypoxia. This study was removed from further analysis, so it is not present in the Tab. 1.
4. Cognitive detriment was noticed in simulated altitude equivalent to 4500 m [22]. 11 non-pilot male subjects took part in this experiment. They went through neuropsychological assessments and emotional functioning tests twice: in normoxia as baseline and after 24 hrs of hypoxia. Significant differences between baseline and experimental conditions were observed. After exposure to 4500 m WM performance decreased in forward as well backward Digit Span tests. ES calculation indicated that the significance was really strong in the forward test (Hedges'  $g = 3.2$ ) and rather strong in the backward test (Hedges'  $g = 0.8$ ). Interestingly, it was observed that exposure to hypoxia affects not only neuropsychological functioning, but also emotional architecture and sleep patterns.

5. Asmaro et al. [1] also took into account working memory performance at baseline and after exposure to two different hypoxic conditions in hypobaric chamber: altitudes equal to 5334 m and 7620 m. The group consisted of 35 objects: mainly pilots (83% of the sample) and a minority of other aviation employees. Similarly to other studies they tested working memory performance with Digit Span Task (forward and backward). At the lower altitude (5334 m) moderate ES was noted for the forward task (Hedges'  $g=0.5$ ) and stronger the backward task (Hedges'  $g=0.9$ ). At higher altitude (7620 m) the power of ES was impressive in both types of tasks: Hedges'  $g=1.39$  for forward and  $g=1.81$  for the backward task. Achieving both altitudes diminishes working memory processing significantly, wherein the strongest ES was observed in the backward tests. ES analysis supports the thesis that Digit Span tasking requires allocation of cognitive resources and the backward test is much more demanding for working memory reserve than the forward one.
6. One of the newest studies carried out in Poland, conducted in the Military Institute of Aviation Medicine [45] also confirms the effects of hypoxia on executive functioning. The objects (paratroopers) were exposed to hypoxia at simulated altitude of 7500 m in hypobaric chamber. Before (pretest) and after (posttest) hypoxia exposure, the cognitive performance was tested using Stroop Task (ST) as well as Reverse Stroop Task (RST). Interestingly, reaction time after hypoxia exposure was faster but it may be due to the effect of learning, which is common for cognitive tasks. Nevertheless, susceptibility to interference effect in RST was stronger after hypoxia exposure. Further analysis revealed that effect size is close to moderate (Hedges'  $g = 0.41$ ). This study confirms that hypoxia exposure can be detrimental to global executive functioning not only in the WM storage and processing domains, but also with regard to inhibition as well as shifting. Those two latter functions take part in higher cognitive processes, so it is assumed that their impairment can lead to endangerment of safety in the air due to decreased decision-making abilities.
7. The highest-altitude hypoxia exposure (10000 m) was the object of the study by Malle's et al. [24]. All the subjects ( $N=57$ ) were pilots attending hypoxia awareness training. The control sample ( $N=29$ ) and experimental

sample ( $N=28$ ) were solving cognitive tasks in neurocognitive assessment battery *Paced Auditory Serial Addition Test* (PASAT). For the study, digit numbers presentation was used as a tool and the subjects' task was to sum every two last digits. In each trial, the participant had to give a response before next digits appear. The experimental group experienced acute hypoxia in a hypobaric chamber and solved PASAT working-memory task at the altitude of 10000 m. Control group also stayed in the hypobaric chamber in order to ensure the same study conditions, but the chamber's door remained open. Analysis indicated that hypoxic exposure significantly affected working memory function. Although the ES for those results was impressive (Hedges'  $g>13$ ) this study had to be excluded from further analysis due to the fact that provided data was expressed as a percentage of correct answers, which was different from the units used in the remaining studies.

### Data analysis

In order to study how hypoxia affects working memory performance the author used a procedure described by Cohen [9,17]. Based on the data provided by the study authors: means and standard deviations the ES was computed (Hedges'  $g$ ) by using an online calculator (available on website: <http://www.polyu.edu.hk/mm/effectsizafaqs/calculator/calculator.html>). Subsequently, a method presented by Hedges and Olkin [14] was used to compute the mean ES and corresponding 95% confidence interval (CI). The meta-analysis was carried out entirely in the R Project for Statistical Computing.

From all distinguished studies, three had to be removed from further analysis in order to avoid distortion of the results. The first was the altitude experiment from Bartholomew's [3] study. Results presented in this paper are unsuitable for calculation because the author failed to provide the values from the pretest in the experiment. Hence, this data has not been included in further analysis. The second was Komiyama's study with insignificant results [19]. The last was Malle's et al. [24] study where only the percentage values were provided.

### RESULTS

Analyzed data set showed high heterogeneity ( $\tau^2=2.77$ ;  $Q(13)=210.955$ ;  $p<001$ ;  $I^2=97.04$ ). Overall effect size (OES) computed in a random model was 1.75 (95% CI=0.85-2.65);  $p<0.001$  (Fig. 1).

Tab.1. Working memory performance after hypoxia exposure at various altitudes.

Study	Objectives <sup>1</sup>	N <sup>2</sup>	Hypoxia induction <sup>3</sup>	Task <sup>4</sup>	Altitude <sup>5</sup>	Pretest M(SD)	Posttest M(SD)	W <sup>6</sup>	g <sup>7</sup>
Legg et al., 2014 [19]	Non pilots	25	Gas mixture	Multiple memory task	2430	41.8(10.5)	2.9(4.2)	0.30	4.78
						0.9(4.6)	0.9(4.6)	0.32	4.97
Bartholomew [3] et al., 1999	Pilots	11	Hypobaric chamber	Digit Span (forward)	3800	10.0(1.91)	8.9(2.0)	0.02	0.56
						12.2(0.91)	7.70(1.63)	0.42	3.28
Lemos [20] et al., 2012	Non pilots	11	Normobaric chamber	Digit Span (backward)	4500	7.9(1.52)	6.9(0.73)	0.19	0.81
				Corsi Blocks (forward)		8.2(1.81)	4.6(0.84)	0.32	2.45
				Corsi Blocks (backward)		9.7(1.15)	5.10(1.28)	0.48	3.64
Bartholomew [3] et al., 1999	pilots	72	Hypobaric chamber	Digit Span (forward)	4570	10.0(1.91)	9.4(2.48)	0.02	0.27
Asmaro [1] et al., 2013	83% pilots, 17% other aviation employees	35	Hypobaric chamber	Digit Span (forward)	7620	6.85(0.94)	3.90(2.12)	0.06	0.51
				Digit Span (backward)		6.06(1.39)	3.61(1.28)	0.06	0.99
Zieliński [45] et al., 2015	Paratroopers	29	Hypobaric chamber	Classic Stroop Task	7500	300.12(181.26)	283.19(103.66)	0.06	0.12
				Reverse Stroop Task		65.22(93.66)	103.66(78.88)	0.07	0.43
Asmaro [1] et al., 2013	83% pilots, 17% other aviation employees	35	Hypobaric chamber	Digit Span (forward)	7620	6.85(0.94)	3.90(2.12)	0.07	1.78
				Digit Span (backward)		6.06(1.39)	3.61(1.28)	0.08	1.82

- 1 subjects: note that paratrooper due to hypoxia experiences have been considered as pilots group
- 2 number of subjects
- 3 manner of hypoxia induction
- 4 WM assessment task
- 5 altitude of hypoxic experience
- 6 weight of the study in meta-analysis
- 7 SE of the study in meta-analysis

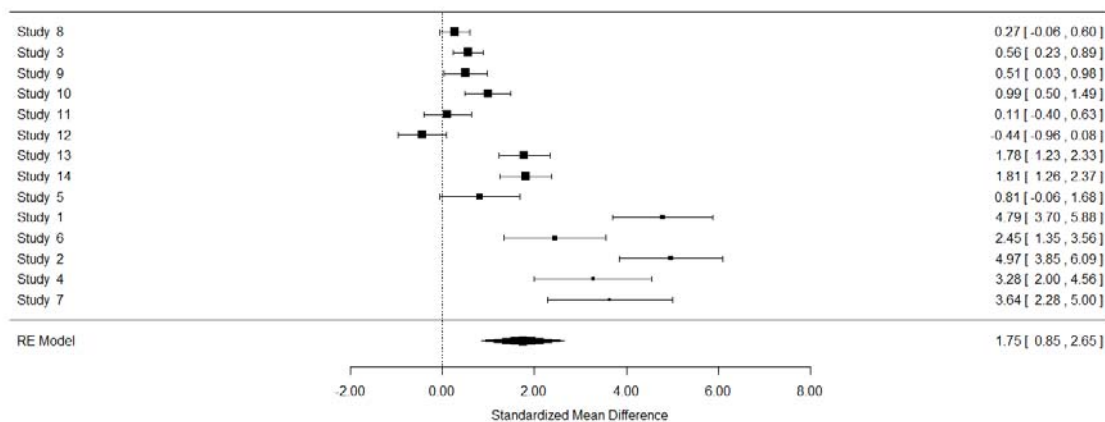


Fig. 1. Overall effect size for analyzed studies.

Tab. 1 presents the weight and ES for every analyzed study. Some additional data from studies have been distinguished.

Fail-safe technique was used to indicate how many insignificant results are needed to halve the effect in the conducted meta-analysis [32]. It was observed that 14 additional results with insignificant p value would halve the ES. Taking into account that this is equal to the quantity of input data to meta-analysis it can be suspected that the OES is overestimated.

In order to detect the source of overestimation of overall effect size of all analyzed studies, author

decided to compare ES obtained from pilots and non-pilots to test whether any of those groups increase general results as an artifact. Welch's T test (unequal variances) indicated that the difference between two groups of subjects is significant ( $t=-3.7885$ ,  $df=6.947$ ;  $p=0.006$ ). Mean ES in pilots was significantly lower (Hedges'  $g=0.699$ ) than in non-pilots (Hedges'  $g=3.321$ ). Funnel plot presents the distribution of distinguished two groups of studies: triangular icons symbolize ES of pilots' studies, whereas round icons regard to ES of non-pilot studies (Fig. 2).

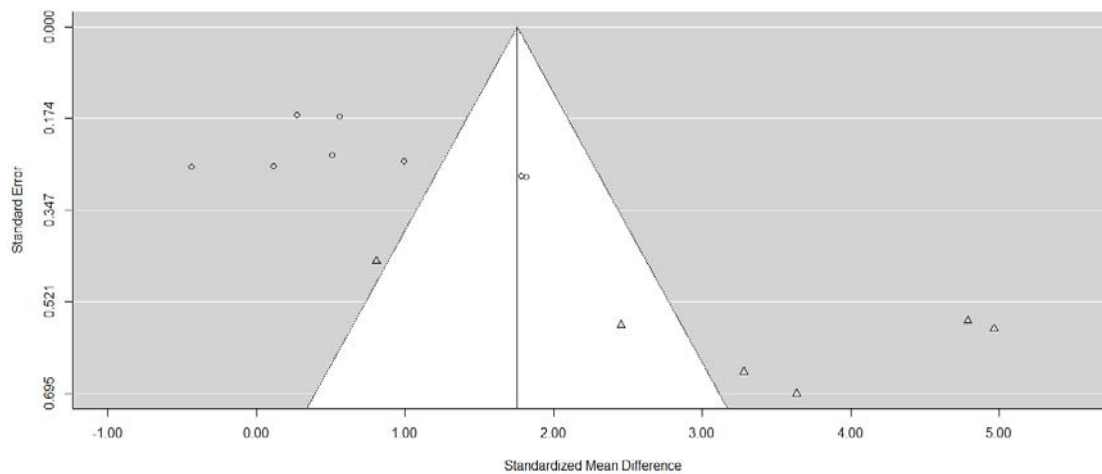


Fig. 2. Funnel plot for ES in pilot and non-pilot subjects.

## DISCUSSION AND CONCLUSIONS

The main aim of this paper was to empirically review studies on WM vulnerability to hypoxia exposure at various altitudes and under various hypoxic conditions. The main hypothesis has been confirmed - hypoxia impairs working memory performance and alters its capacity above 3800 m altitude. Overall effect size seems impressive, but it can be suspected that it is overestimated. It is worth considering those results in two separate groups of studies, which were qualitatively different: in pilots and non-pilots. After dividing the groups it is noticeable that the magnitude of the ES was determined by non-pilot studies, which increase the OES.

If pilots were less vulnerable to working memory alterations caused by hypoxia, the facilitating role of experience, which possibly builds up and enhances resistance to the impact of high altitude, should be discussed in future research. On the other hand, pilots have to deal with cognitive performance assessment more often than the general population, which may result in appearance of learning effects, particularly when they train performance of the same or similar task under different conditions, such as high-G training.

As fail-safe technique indicated, the same amount of insignificant studies would reduce the effect size. Due to publication bias, many research studies showing insignificant differences in WM performance under differentiated hypoxic condition have not been published. Studies with impressive results are available, leading to overestimation of the general effect. The limitation of this meta-analysis is a small number of considered

studies, which prevents comparison between other distinguished variables: simulated flight level, manner of hypoxia induction or type of cognitive task. Open access to all results – those presenting influence as well as those that show lack of impact of hypoxic conditions on cognitive performance provide more reliable results.

Nevertheless, some directions for future research may be outlined. Although presented studies deliver some data about cognitive functioning under hypoxia, we still know very little about specific WM components. Not only vast amount of future research needs to be done in this area of interest, but also researchers should focus on some specific working memory and executive functions aspects as well. There is still a shortage of studies on cognitive susceptibility to oxygen storage, which would distinguish between particular WM components in Baddeley's model. Most of the presented studies were focused on phonological loop functions (for instance: Digit Span - forward and backward, Free Recall Task). Others were conducted with tools used for inhibition assessment, such as Stroop Task, where WM performance is tested only indirectly and the object has to follow and actualize task instructions. As mentioned at the beginning, WM consists of one prominent (central executive) and few subordinate elements like phonological loop, visuospatial sketchpad and episodic buffer. Because of individual properties of each of those components, there is a need for studying their vulnerability to hypoxia separately, not only as a single construct. For instance, phonological loop performance and potential

impairment due to hypoxia may play a vital role while listening to auditory commands and news from air traffic control. Otherwise, visuospatial sketchpad performance may influence perceptual processes and its impairment may mediate spatial disorientation in hypoxia experience.

The value of the presented study contains not only in the results for cognitive tasks performance, but also in some other observations, which may be essential to understanding how hypoxia affects pilot performance. There are some non-cognitive consequences of hypoxia exposure, which may trigger changes in cognitive processing indirectly, as a mediator. For instance, some studies revealed that participants were completely unaware of their cognitive detriments and worsened performance after hypoxia exposure. Nonetheless, their behaviors and emotional states were rapidly changing with subsequent flight levels. At 5334 m, they were rather euphoric and declared well-being observing no decrease in cognitive performance. Unrealistic optimism due to increasing positive mood is an essential threat related to hypoxia exposure. As Makarowski and Smolicz noticed [23], euphoric state involving decrease of criticism is a dangerous consequence of hypoxia, which may lead to overlooking potential threats. Under such circumstances situational judgment of risk may be decreased as well. There is an effect called perceived invulnerability [21,37]. Moreover, as hypoxia exposure increases positive mood and arousal, it may weaken working memory performance. According to Orzechowski [33] positive effect may impair WM performance because of involvement of cognitive resources in the processing of information related to mood. However, another current theory in the literature assumes informative aspect of experienced mood. Hence, one's awareness and attention concentrate on processing information related to negative affect, which in consequence reinforces executive functioning and, obviously, WM performance. Otherwise, positive affect may reduce processing and in consequence one's attention is not drawn to risk or a possible threat.

As for other non-cognitive detriments, long-term consequences are also observed with regard

to the sleep-pattern changes after high-altitude exposure [22,36]. Those alterations particularly concerned decreased slow-wave sleep and rapid eye-movement (REM) sleep, frequent awakenings and sleep fragmentation. This can worsen cognitive performance as well as well-being, making those alterations an indirect effect of hypoxia.

There are certainly some unrecognized factors that might foster experiencing cognitive consequences of hypoxia. Some research studies postulate that potential risk lies in fatigue. This underestimated but noticeable element may mediate the relationship between high altitude exposure and WM performance by triggering alterations in reaction time and psychomotor performance.

The last conclusion considers the methods of cognitive assessment. There is no one universal tool to test executive function and working memory capacity and the presented studies were conducted with various methods. The most common tool was Digit Span: forward (6 studies) and backward (4 studies). Other studies were totally different and could be used to measure other executive functions as well, but including only the studies utilizing Digit Span test would make the meta-analysis impossible. Executive function assessment is susceptible to learning and the results obtained after performing one test at baseline and another under experimental conditions are often distorted by learning processes. One of the most popular cognitive assessment tool in aviation, CogScreen was used in Hewett et. al [15] study on American soldiers to test cognitive deterioration under hypoxic condition (induced by ROBD gas mixture). They used it to test the ability to divide attention, matching to sample, pathfinder combined and visual sequence comparison - subtests relating to cognitive functions other than working memory performance. Interestingly, no significant difference except slightly worsened vigilance was observed in cognitive functioning between baseline and experimental conditions at altitudes from 2400 to 4200 m. Possibly, such result is a consequence of the order effect; this measure may be not sensitive enough to detect subtle alterations in cognitive control.

## AUTHOR'S DECLARATION:

**Study Design:** Marta Molińska; **Data Collection:** Marta Molińska; **Statistical Analysis:** Marta Molińska; **Manuscript Preparation:** Marta Molińska; **Funds Collection:** Marta Molińska. The Author declares that there is no conflict of interest.



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