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# *Cognition and neuropsychological changes at altitude – a systematic review of literature*

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## Abstract

**Background:** High-altitude exposure is widely accepted to affect cognitive functions. Yet, studies investigating altitude-related effects on the cognitive domain have yielded in inconsistent results. One reason for this was thought to be the difficulty of comparing test designs and the breadth of the neuropsychological tests used. According to published reports, relative altitude as well as duration of altitude exposure seem to have the greatest impact on cognition. Moreover, sufficient acclimatization appears to have a beneficial effect on cognitive functions at altitude. To date, several assessment techniques have been developed to monitor cognitive functions in high-altitude studies. The aim of the current study is to evaluate the effects of altitude exposure on cognitive functions in healthy subjects, and to provide a structural overview of the applied neuropsychological tests used to obtain these results.

**Methods:** A comprehensive literature search was performed using PubMed up to October 2021 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Eligibility criteria included a healthy human cohort exposed to altitude in the field (at minimum 2,440 m) or in a hypoxic environment in the laboratory ($F_iO_2$ corresponding to at minimum 2,440 m) and outcome of cognition with an experimental design.

**Results:** The literature search identified 123 articles, of which 52 articles were included in the systematic review. The examined altitudes ranged between 2,440 m and 8,848 m. Of the 52 published studies, 29 examined the impact of altitude in the field. All other studies conducted hypoxia research in laboratory settings. Researchers applied 112 different neuropsychological tests, with a total of 173 test applications on subjects. Furthermore, neuropsychological tests were classified depending on their superordinate cognitive domains naming their outcomes, the investigated altitudes, and the intervention methods. Attentional capacity, concentration and executive functions proved to be the most frequently studied cognitive domains. Analysis of the results revealed that less than half of the applied neuropsychological test showed significant impairment at the examined altitudes. Of all the neuropsychological tests that were conducted in the field, 66.4 % showed no impairment or even improvement while 33.6 % found significant deteriorations at high altitude. In the laboratory setting, these results were reversed with 64.7 % of tests showing deterioration, while 35.3 % test showed no or improved effects. Only a few articles used measures such as control groups or alternative test forms in repeated measure testing to control for learning effects. The majority of articles discussed learning effects as a potential source of error. The *Stroop Test* was used most frequently and appeared to be more

sensitive in laboratory studies compared to field studies. The *Psychomotor Vigilance Test* revealed significant impairment between the altitudes of 3,269-3,800 m and the *N-Back Number Task* between 3,800-4,500 m.

**Conclusion:** Here we provide a systematic literature review on articles that investigated cognitive function at altitude. One main purpose of this review was the classification of the used neuropsychological tests, and their aptitude for detecting impairment of cognitive performance at altitude. Referring to the current state of research, to our knowledge, this is the first overall review that explicitly mentions the applied neuropsychological tests, classifying them into supercategories according to their cognitive domain, and listing their results in terms of the investigated altitudes. We found that in the neuropsychological tests performed in the laboratory, the ratio of results that showed altitude-induced impairments was twice as high compared to those showing no changes or improvements. Studies conducted in the field yielded in the opposite results consistent with the idea that sufficient acclimatization has beneficial effects on cognitive functions at high altitude. The analysis of the published data demonstrates the need for a common consensus on study design, and the use of a standardized framework of tests, for instance by creating an open access test battery. The STAR guidelines for data reporting have proved useful in assessing study quality, and their utilization in future studies may contribute to further standardization of methods.

**Keywords: altitude, hypoxia, neuropsychological tests, cognitive domains, cognition, PRISMA, STAR data reporting guidelines**

## Zusammenfassung

**Hintergrund:** Es ist weithin anerkannt, dass eine Exposition in großer Höhe die kognitiven Funktionen beeinträchtigt. Allerdings haben Studien, die höhenbedingte Auswirkungen auf den kognitiven Bereich untersuchten, zu widersprüchlichen Ergebnissen geführt. Ein Grund dafür ist wahrscheinlich die schwierige Vergleichbarkeit der Testdesigns und die Bandbreite der angewandten neuropsychologischen Tests. Den veröffentlichten wissenschaftlichen Berichten zufolge scheinen sowohl die relative Höhe als auch die Dauer der Höhenexposition die größten Auswirkungen auf die Kognition zu haben. Darüber hinaus scheint eine ausreichende Akklimatisierung einen günstigen Effekt auf die kognitiven Funktionen in der Höhe zu haben. Bislang wurden mehrere Untersuchungsmethoden entwickelt, um kognitive Funktionen in Untersuchungen in der Höhe zu erfassen. Ziel der vorliegenden Untersuchung ist es, die Auswirkungen der Höhenexposition auf die kognitiven Funktionen gesunder Probanden zu evaluieren und einen strukturellen Überblick über die angewandten neuropsychologischen Tests zu erstellen, die zur Erlangung dieser Ergebnisse eingesetzt wurden.

**Methoden:** Es wurde eine umfassende Literaturrecherche in PubMed bis Oktober 2021 gemäß den Leitlinien Preferred Reporting Items for Systematic Reviews and Meta-Analyses durchgeführt. Zu den Eignungskriterien gehörten eine gesunde menschliche Kohorte, die einer Höhe im Feld (mindestens 2.440 m) oder einer hypoxischen Umgebung im Labor (FiO2, der mindestens 2.440 m entspricht) ausgesetzt war, sowie Ergebnisse zur Kognition in einem experimentellen Rahmen.

**Ergebnisse:** Die Literaturrecherche ergab 123 Artikel, von denen 52 Artikel in die systematische Übersicht einbezogen wurden. Die untersuchten Höhenlagen lagen zwischen 2.440 m und 8.848 m. Von den 52 veröffentlichten Studien untersuchten 29 die Auswirkungen von Höhe im Feld. Alle anderen Studien führten Hypoxieuntersuchungen im Labor durch. Die Forscher wandten 112 verschiedene neuropsychologische Tests an, mit insgesamt 173 Testanwendungen bei den Testpersonen. Darüber hinaus wurden die neuropsychologischen Tests nach ihren übergeordneten kognitiven Domänen klassifiziert, wobei die Ergebnisse, die untersuchten Höhenlagen und die Interventionsmethoden genannt wurden. Aufmerksamkeitsleistung, Konzentration und exekutive Funktionen erwiesen sich als die am häufigsten untersuchten kognitiven Domänen. Die Analyse der Ergebnisse ergab, dass sich bei weniger als der Hälfte der angewandten neuropsychologischen Tests eine signifikante Beeinträchtigung in den untersuch-

ten Höhenlagen zeigte. Von allen neuropsychologischen Tests, die im Feld durchgeführt wurden, wurden bei 66,4 % keine Beeinträchtigung oder sogar eine Verbesserung festgestellt, während bei 33,6 % eine signifikante Verschlechterung in großer Höhe beobachtet wurde. Im Labor kehrten sich diese Ergebnisse um: 64,7 % der Tests wiesen eine Verschlechterung auf, während 35,3 % der Tests keine oder verbesserte Auswirkungen ergaben. Nur in wenigen Artikeln wurden Maßnahmen, wie Kontrollgruppen oder alternative Testformen, bei der wiederholten Testdurchführung zur Kontrolle von Lerneffekten eingesetzt. In der Mehrzahl der Artikel wurden Lerneffekte als eine potenzielle Fehlerquelle diskutiert. Der *Stroop-Test* wurde am häufigsten verwendet und schien in Laborstudien empfindlicher zu sein als in Feldstudien. Der *Psychomotorische Vigilanztest* zeigte eine signifikante Beeinträchtigung zwischen 3.269 und 3.800 m Höhe und der *N-Back Number Task* zwischen 3.800 und 4.500 m.

**Schlussfolgerung:** Die vorliegende Arbeit enthält eine systematische Literaturübersicht über Artikel, welche die kognitiven Funktionen in der Höhe untersucht haben. Ein Hauptziel dieser Übersichtsarbeit war die Klassifizierung der verwendeten neuropsychologischen Tests und deren Eignung zur Feststellung von Beeinträchtigungen der kognitiven Leistungsfähigkeit in der Höhe. Nach unserem Kenntnisstand ist dies die erste Übersichtsarbeit, die explizit die verwendeten neuropsychologischen Tests auflistet, sie nach ihrer kognitiven Domäne in Überkategorien einteilt und deren Ergebnisse in Bezug auf die untersuchten Höhen auflistet. Wir haben festgestellt, dass bei den im Labor durchgeführten neuropsychologischen Tests der Anteil an Ergebnissen, die höhenbedingte Beeinträchtigungen aufwiesen, doppelt so hoch war wie der Anteil jener, die keine Veränderungen oder Verbesserungen zeigten. Studien, die im Feld durchgeführt wurden, ergaben entgegengesetzte Resultate, die mit der Annahme übereinstimmen, dass eine ausreichende Akklimatisierung positive Auswirkungen auf die kognitiven Funktionen in großer Höhe hat. Die Analyse der veröffentlichten Daten zeigt, dass ein gemeinsamer Konsens über das Studiendesign und die Verwendung einer standardisierten Testpalette erforderlich ist, zum Beispiel durch die Schaffung einer öffentlich zugänglichen Testbatterie. Die STAR-Leitlinien für die Datenberichte haben sich bei der Bewertung der Studienqualität als nützlich erwiesen, und ihre Anwendung in künftigen Studien könnte zu einer weiteren Standardisierung der Methoden beitragen.

**Schlagwörter: Höhe, Hypoxie, Neuropsychologische Tests, Kognitive Domänen, Kognition, PRISMA, STAR-Leitlinien für die Datenberichte**

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## Abbreviations

| | |
|---|---|
| A | Active mode of ascent |
| APTS | Automated Performance Test System |
| ASL | Above sea level |
| AMS | Acute mountain sickness |
| ANAM | Automated Neuropsychological Assessment Metric |
| A-DST | Auditory Digit Span Test |
| BART | Balloon Analogue Risk Task |
| BCA | Baseline cognitive assessment |
| BHG | Breathing of hypoxic gas mixture |
| CA | Cognitive assessment |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CG | Control group |
| CMS | Chronic mountain sickness |
| COPD | Chronic obstructive pulmonary disease |
| CPT | Continuous Performance Test |
| DANA | Defense Automated Neurobehavioral Assessment Test Battery |
| dSRT | Change score = SRT1 minus SRT2 |
| DSST | Digit Symbol Substitution Test |
| DST | Digit Span Test |
| DST-F | Digit Span Test Forward |
| DST-B | Digit Span Test Backward |
| EPO | Erythropoetin |
| F | Female |
| $F_iO_2$ | $O_2$ volume fraction |
| FT | Field test |
| HACE | High-altitude cerebral edema |
| HAPE | High-altitude pulmonary edema |
| Hb | Hemoglobin |
| HH | Hypobaric hypoxia |
| HHC | Hypobaric hypoxia chamber |
| HIF-1α | Hypoxia-inducible factor 1α |
| HVR | Hypoxic ventilatory response |

| | |
|---|---|
| Impact of altitude ↔ | No effects, unchanged performance |
| Impact of altitude ↑ | Increased performance |
| Impact of altitude ↓ | Reduced performance |
| LT | Laboratory test |
| M | Male |
| NA | Information not available |
| NH | Normobaric hypoxia |
| NHC | Normobaric hypoxia chamber |
| NO | Nitric oxide |
| P | Passive mode of ascent |
| $p_aCO_2$ | Arterial carbon dioxide partial pressure |
| PASAT | Paced auditory serial addition test |
| $p_aO_2$ | Arterial oxygen partial pressure |
| $p_AO_2$ | Alveolar oxygen partial pressure |
| $P_B$ | Barometric pressure |
| $p_iO_2$ | Inspiratory oxygen partial pressure |
| PVSAT | Paced visual serial addition test |
| PVT | Psychomotor Vigilance Test |
| RMCPT | Running Memory Continuous Performance Test |
| RFFT | Ruff Figural Fluency Test |
| $S_aO_2$ | Arterial oxygen saturation |
| SL | Sea level |
| SRT | Simple reaction time |
| V-DST | Visual Digit Span Test |
| $VO_2max$ | Maximal oxygen consumption |
| VWMC | Verbal Working Memory Capacity |

# 1. Introduction

Mountaineering as a recreational activity has enjoyed rising popularity in the last century even conquering the mass-market with sports such as hiking and skiing. Redirecting one's focus of recreation from the cities and back to nature is one of the trends of the 21st century. A whole industry has recognized the underlying potential to such an extent that tourism has now outreached common vacation areas, expanding also to life jeopardizing regions like the Himalaya in a commercial way. Consequently, a rising number of individuals find themselves in high-altitude environments. This, in turn, also leads to more accidents taking place for which mountain rescue and salvage operations are needed. By looking at what exactly is jeopardizing while living or moving in altitude, it becomes apparent that there are external factors conditioned by terrain for example avalanches, rockfall or cold. Furthermore, reduced oxygen partial pressure can evoke possibly life-threatening diseases for example acute mountain sickness (AMS) [1], high-altitude pulmonary (HAPE) [2], or cerebral edema (HACE) [3], which will be described further in Chapter 1.2.3. Another hazard is the individual's performance of risky behavior, especially when climbing or performing in terrain with a risk of falling. In this respect, solid cognitive abilities with sufficient accountability seem essential to assess potential dangers or dangerous behaviors and to be able to avert these in time. Previous observations in this area have also shown a connection between impaired mental capacity and reduced oxygen partial pressure (see also Chapter 1.3). However, a clear cause-and-effect detection is yet outstanding.

This dissertation is a review article providing a structural overview of studies that aimed to investigate cognitive functions and possible impairments at altitude, either through field or laboratory studies, such as altitude chambers or hypoxic gas mixture breathing, respectively. In the theory part, cognitive functions and factors influencing such processes are presented in more detail. Afterwards, physiological circumstances of altitude and potential altitude-induced medical problems will be examined. This is followed by the effects of altitude on cognition and the currents state of research. The selection and analysis of these studies will be explained in the methods section, before demonstrating the findings in the results section and further providing a list of the cognitive domains investigated and the tests used. Then, the results will be critically discussed, and limitations of this work will be mentioned. Finally, implications for future research will be pointed out.

## 1.1 Cognition

### 1.1.1 Cognitive functions

Cognitive functions can be subdivided into four major classes, analogous to the computer operations of *input*, *storage*, the *processing* containing sorting, combining and allocating information in several ways, and eventually *output* [4]. Correspondingly *(1) receptive functions* comprise the skills of sensory reception and perception which involves the processing of sensations like selection, acquirement, classification and integration of information; *(2) memory and learning* involve the storage and retrieval of information and consist of the declarative (explicit) memory and the nondeclarative memory. Explicit memory roughly contains three stages with sensory store, immediate memory, which holds short-term memory, and long-term memory. The working memory is seen as an operative set of subsystems with immediate memory and a restricted capacity executive system, which is used for a limited time frame for storing and processing cognitive operations or problem solving.; *(3) thinking* refers to the mental organization and reorganization of information; and *(4) expressive functions* are the means by which information is communicated or implemented, so to speak the sum of observable behavior. Each function class includes many subtle purposes - for example, color perception or instant-memory for verbal content. Although each function class represents a distinct set of activities, they usually work in a close, interactive relationship with one another.

### 1.1.2 Mental activity variables

The activity of cognitive functions is supported and maintained to some extent by attentional functions, classified as *mental activity variables* [4]. Referring again to computer operations, they serve to some extent as operation commands appointing one or more cognitive functions. Mental activity variables have to do with the efficiency of mental processes and can be described as behavior characteristics. They are closely engaged in cognitive operations, without having a singular behavioral end product and can be grouped into the categories level of *consciousness*, *attentional functions* and *activity rate* [4].

#### *Consciousness*

Today we are still on the way to approaching a definition of what we might understand by "consciousness" and the discourse on this is in a state of full progress [5]. Still, it is commonly

accepted that consciousness refers to an organism's level of being awake or receptive to stimulation. Often the term consciousness is misleadingly used to describe the state of being aware of oneself or one's surroundings, a setting in which the word awareness should be used [4].

#### *Attentional functions*

Attention concerns abilities or processes of how the organism is susceptible to excitations and how it can start processing received or observed stimuli, be it internal or external. Two main aspects of attention include automatic processes, reflex, and controlled processes, so to say voluntary. Other characteristics are that attention has restricted capacity and it includes both perceptual and inhibitory processes. In summary the following four aspects of attention are of greater research interest: (1) Focused or selective attention, also known as concentration, to maintain attention at a high stimulus frequency; (2) Vigilance as a state of sustained attention at a monotonous stimulus frequency; (3) Divided attention as the ability to respond to multiple elements within a complex mental task; (4) Alternating attention with a responsive shifting to match focus and tasks [4].

#### *Activity rate*

Activity rate includes the execution speed of mental activities as well as the motor responses. A slowing down of mental activity is therefore mainly visible in delayed reaction times. It must be mentioned that a number of upstream mechanisms can be responsible for a slowdown, e.g., poor concentration, low-performance accuracy or reduced auditory span [4].

#### *Executive functions*

According to Lezak [4], executive functions, together with cognition as the information-processing part and emotionality, which includes feelings and motivation, belong to the three functional systems of behavior. Executive functions have to do with *how* behavior is expressed and enable a person to perform unconditional, goal-oriented, autonomous, and self-sufficient behavior. Conversely, this understanding is opposed to the supercategory of the cognitive domain "executive function" used in the following. Thereby, reference is made to the studies reviewed (see [6-8] and so on) that use the term executive function in connection with neuropsychological tests requiring the management and close interaction of different mental abilities. In this sense, it is necessary to use the term beyond its original definition, which is hereby pointed out.

### 1.1.3 Factors with an influence on cognitive functions

If the flow of information to the brain via the external sensory channels is prevented or drastically restricted, for instance, in the context of sensory deprivation, changes occur at all levels

of perception and behavior. By contrast, sensory and physical hyperstimulation can also lead to major alterations in both perception and behavior [5]. This also includes physical stress that can occur when staying in extreme environmental conditions, such as great altitude, reduced atmospheric pressure, cold temperatures, lack of recreation and sleep as well as movement strains. They can lead to altered states of perception that manifest themselves in acoustic and visual hallucinations, somaesthetic illusions or states that resemble deep hypnosis.

We now turn to the situational conditions that normally occur during expeditions at high altitude.

### Oxygen deprivation

In the case of oxygen deprivation, a distinction must be made between anoxia and hypoxia. Anoxia signifies the entire absence of available oxygen and this, for example triggered by reduced blood flow as in the case of ischemia, leads to anoxemia. The latter, i.e. when the blood leaks oxygen, can be fatal if it persists for more than five to ten minutes [4]. Whereas ischemia involves reduced blood flow, affecting the delivery of glucose, other substances, and oxygen on the one hand, and the removal of metabolic byproducts on the other, a hypoxic episode differs in that cerebral perfusion continues and only the oxygen level is changed [9]. Nevertheless oxygen deprivation, as occurring in the environmental conditions of great altitude and reduced atmospheric pressure specified below, can lead to mental changes if it lasts long enough and is sufficiently severe [4]. This review excluded articles on studies conducted with military personnel or aircrew and those conducted with long-term residents of high altitudes. The effects of acute hypoxia exposure, such as regularly experienced by aircrew or military personnel, is of great interest to this industry. Since hypoxia is considered one of the greatest single hazards during high-altitude flight, the aviation industry is conducting extensive research to determine factors and neuropsychological effects to prevent potentially serious consequences such as hypoxic incidents during flights or missions [10, 11]. While brief hypoxia was found to be relatively benign [12], continuing or frequently recurring hypoxic episodes are also associated with brain damage [13-15]. In view of prolonged hypoxia through chronic high-altitude exposure, as is the case with permanent altitude dwellers, the question of neuropsychological impairments is difficult to answer and data is scarce [16]. However, there is evidence that the mental abilities of long-term high-altitude residents are impaired compared to those of people residing at sea level. Thus, presumably comparable groups of infants, children, and adolescents living at altitudes of about 500 m, 2.500 m, and 3.700 m in Bolivia were studied, showing a decrease in

motor speed, cognitive processing speed, and cerebral blood velocity with increasing altitude [17]. As causative factors, a direct effect of hypoxia on brain function or a slower development of the central nervous system in the hypoxic environment was discussed [18]. Also worth mentioning at this point are epidemiological studies suggesting that Chronic obstructive pulmonary disease (COPD) increases the risk of cognitive impairment. In addition to hypoxic components such as hypoxemia as a direct result of respiratory impairment, other pathological mechanisms such as structural brain changes are suspected to be the cause [19]. The latter are thought to be due to risk factors such as smoking and hypertension, which are more common in individuals with pulmonary disease and are themselves known to negatively affect cognition [20]. In addition, cognitive impairment was found to be related to the profile of COPD severity and comorbidities. The most commonly studied cognitive domains are memory and attention and patients with COPD show significant impairments in these domains among others [21]. With the brain being more dependent on constant oxygen supply than many other tissues, there are some brain areas that are especially susceptible to oxygen depletion. To some extent due to their distal position in the vascular distribution [4], this includes the hippocampus, basal ganglia, and the cerebral cortex [22, 23]. Regarding hypoxia, the current state of research will be discussed later in Chapter 1.3.2.

#### *Cold stress*

Cold leads to physiological changes in individuals, such as centralized blood circulation due to vasoconstriction and, in the case of prolonged cold, subsequently to lower core temperature, a drop in blood pressure and muscle shivering to prevent hypothermia. In the review by Martin et al. [24] the effects of cold stress on cognitive or military task performance were investigated, among other ways, by analyzing twenty studies. It was found to have little influence on attention and processing speed, but a mixed influence on working memory and executive actions. By contrast, an increasingly negative influence of cold stress on military task performance was found regarding function of task complexity. The authors saw the distracting effect of cold sensations as causal for the negative effect on cognitive performance since the attention of an individual is redirected when faced with thermal discomfort and thus diverted from the actual task. Besides, they also mention that the studies indicate a reduction of negative effects of cold on performance as a result of cold habituation and familiarity to a given environment. Another systematic review by Falla, Micarelli, Hüfner, and Strapazzon [25] focusing exclusively on the effects of cold on cognitive performance has identified 18 studies that examined the effects of exposure to cold air or immersion in cold water. They found that cold exposure resulted in

impairment in most of the studies analyzed, with the affected cognitive domains being attention and processing speed, executive functions, and memory in particular.

The combination of cold stress and altitude confronts the body with additional challenges [26]. On the one hand, energy expenditure at altitude is additionally increased in cold ambient temperatures [27]. A lack of oxygen produced by the lowered inspiratory oxygen partial pressure ($p_iO_2$) can delay the initiation of vasoconstriction and shivering thermogenesis, thereby promoting the onset of cooling and the development of hypothermia [28]. The respiration also faces some challenges, because both the cold and the altitude can contribute to constriction of the pulmonary vessels and thus provoke pulmonary hypertension or even the development of pulmonary edema [29]. Enhanced respiratory activity at altitude, initially as a reactive compensation for oxygen deficiency, leads in the presence of cold stress to increased respiratory water as well as heat loss and respiratory symptoms. Inhalation of cold air through the nose is less likely to lead to reduced respiration in humans compared to animals in terms of relative hypoventilation [30], but may theoretically lead to higher oxygen desaturation of the blood and thus to reduced performance [26].

### *Sleep deprivation*

An individual must be awake and conscious to be able to focus attentional resources for a substantial period of time in order to adequately process complex cognitive tasks. Given this, sleep loss - be it just one night of sleep deprivation - appears to have the most consistent and profound effects on various aspects of cognitive function, such as simple wakefulness, attention, and psychomotor vigilance. These impairments include inconsistent and slowed responses; moreover, various sensory systems may be impaired by sleep loss. Memory processing also appears to be impaired during sleep deprivation due to difficulties in encoding new information. Lack of sleep after studying leads to impaired consolidation of memories and subsequent retrieval [31]. Another profound effect of sleep loss is dysregulation of mood and emotion. In this regard, neuroimaging evidence indicated that sleep deprivation weakens functional connectivity between the brain's inhibitory prefrontal cortex and limbic emotional systems and can lead to dysregulation of these emotional systems [32]. The affective imbalance toward negative mood states may in turn affect other aspects of perception, memory, and higher-level judgments and decisions. This seems to be particularly crucial in mountain behavior with respect to inhibitory control, risk-taking, judgment, and decision-making. Findings showed decreased inhibitory control during the first night of sleep deprivation. Alterations in risk taking seemed to result in both overly optimistic expectations of the possibility of future gains and an underestimation

of the possibility of losses [31]. Although chronic partial sleep restriction is more common than absolute sleep restriction in everyday life, fewer studies have examined its effects on cognitive performance. Partial sleep restriction has been found to affect attention, particularly vigilance [33]. This can be measured, for example, with a high signal load reaction time test, the *Psychomotor Vigilance Test*, which has been shown to be extremely sensitive to sleep deprivation [34].

Regarding sleep at altitude, lowlanders often report poor sleep quality during the first nights after arrival at high altitude, with polysomnographic studies identifying reductions in slow-wave sleep as the most consistent altitude-induced change in sleep structure. This decrease in neuronal synchronization during sleep at altitude also appeared to be associated with a decrease in sleep-related memory consolidation in healthy subjects [35]. The sleep structure as well as the total sleep time are essentially unchanged in high altitude compared to low altitude; however, several stresses of high-altitude mountaineering are causes for sleep disturbances in high altitude. These include high nighttime adrenaline and cortisol levels due to exertion and excitement, unfamiliar or uncomfortable sleep environment, or nocturia due to high-altitude diuresis [36]. Concerning sleep interruptions due to respiratory arousals, the literature contains different data, and whether sleep instability at high altitude is contributory to periodic breathing or vice versa is still unclear [35, 36]. Rapid eye movement sleep and deep sleep in any case decrease slightly in favor of light sleep. In summary, hypoxia seems to be primarily responsible for sleep disturbances at high altitude [36].

### *Physical strain*

Not so long ago, there were hardly any solid empirical studies on this topic and most of the material was of anecdotal nature, but in recent years, there has been growing evidence for the benefits of physical activity on cognitive functioning. And interestingly, this link does not merely go in one direction, there is also evidence that some specific cognitive skills promote an improvement in athletes' performances in competition [37]. The background to this could be the need for constant attention, adaptation to changing situations, or management of multiple variables in high-performance sports [38, 39]. Imaging techniques have revolutionized the visualization and understanding of cognitive processes that arise in physical activity and sport contexts [37]. In addition, the changes in the brain observed by these techniques are complemented by other areas such as considerations from neurobiology and neurophysiology. In this regard, there are hypotheses related to changes at the neuronal level such as neurogenesis, synaptogenesis or angiogenesis, and biomolecules that seem to mediate the benefits of exercise on

cognitive function [40]. In a review by Ando et al. (2020) [41], the effects of acute exercise under hypoxia on cognitive performance are examined in more detail, as moderate intensity exercise under normal conditions has been shown to be beneficial for cognitive performance. This review examines combined effects of acute exercise and hypoxia and considers them to have implications for activities at terrestrial altitudes where cognitive performance is critical. However, the exact physiological mechanisms remain unknown.

Regarding changes in perception due to extreme athletic performance and extraordinary life situations, there is likewise increasing interest. This also includes phenomena of more popular scientific interest, such as the "runner's high." One of the early systematical studies by Brugger, Regard, Landis, and Oelz (1999) [42] retrospectively gathered anomalous perceptual experiences of people who had been at altitudes above 8,000 m without artificial oxygen supply. Almost all mountaineers (7 out of 8) experienced changes in their body schema, this being the most striking somaesthetic phenomenon, which was then followed by visual and acoustic hallucinations. The phenomena occurred more frequently above than below an altitude of 6,000 m and are interpreted by most researchers as consequences of hypoxia, which is aggravated by social deprivation and acute stress [5].

### 1.1.4 Assessment techniques

In this work all neuropsychological tests that have been used in the reviewed articles referring to the issue of cognitive changes in high altitude will be listed. In the categorization, we correspond to the compendium of tests and assessment techniques in Lezak's "Neuropsychological Assessment" (pp. 391), where a more detailed report about each procedure can be found. The functional divisions and categorizations are, to some extent, conceptual constructs that help the investigator understand what is involved in the usually very complex behaviors and test responses of the individuals being studied. Thus, in all the tests mentioned, it should be noted that the cognitive constructs, while theoretically differentiated, can be difficult to separate in reality. Strictly speaking, no test measures a single ability, as the discrete functions hardly occur in isolation and usually add to larger operational patterns developed in the highly spezialized cerebrum [4].

The cognitive domains pertinent to this work are mentioned next to give a brief, yet not exhaustive, overview by referral to the structural outline as proposed by Lezak [4]. If not marked separately, this work was mainly consulted in this context.

### *Orientation*

Orientation for time and place depend on the awareness of self in relation to one's surroundings, presuppose a consistent and reliable integration of perception and attention as well as awareness of the ongoing narrative and thus memory.

Time orientation is important for planning, such as determining when to expect an upcoming event or calculating how long a string of actions will take, and is located primarily in the critical basal ganglia, prefrontal cortex, and medial temporal lobe [43-45].

### *Attention*

Attention, concentration, and tracking are necessary skills for goal directed behavior. As mentioned previously, few tests measure a single cognitive construct; this is particularly the case with tests of attention. Attention functions can only be measured in the context of a cognitive activity sequence, depending on the focus. These would be tests of attention, short-term memory, or working memory. Within this context, attention and the temporary storage of information play an essential role and a common characteristic is them having limited capacity. A superordinate term is therefore attentional capacity. Attention span can for example be investigated with the help of *Span Tests*, where the subject is exposed to alternating amounts of information with the assignment to give an immediate response by repeating what was seen or heard. The size of the correctly contained and reproduced information is indicative of the subject's attentional capacity size.

The working memory, also referred to as mental tracking, can deal with more complex cognitive operations and allows information to be maintained in a temporary storage and be manipulated. This includes an executive control mechanism to focus attention and block out interference [46]. Verbal working memory networks are located in the left dorsolateral prefrontal cortex, whereas the spatial version is found opposite in the right dorsolateral prefrontal cortex [47, 48]. Well known tests are the *Digit Span Backwards* and *Letter-Number Sequencing Test* requiring storage and reorganization.

When examining attention one also considers concentration or focused attention. Many theorists believe that vigilant attention, responding to stimuli in a timely fashion, is the basis for other, more complex components of cognition [34]. Exemplary tests are the *Continuous Performance Test (CPT)* [49] or *Ruff 2 & 7 Selective Attention Test* [50], providing information on sustained attention with reaction times and accuracy data.

Information processing speed is important for many cognitive tasks in order to be able to process the task within the time allowed [51]. Processing speed can be examined with the help of tests of response speed in regards to *Reaction Time* and deceleration is often subject to attentional deficits [52].

Complex attention can be measured via symbol substitution tests, for example *Digit Symbol (Substitution) Tests (DSST)* [53, 54], that next to sustained attention also require visual scanning, visuomotor coordination, motor persistence, and response speed [55].

And finally, one has to mention divided attention, e.g. measured by *Trail Making Tests*. In these tests scanning, visuomotor tracking and cognitive flexibility are also needed as one has to connect consecutively numbered circles (*Part A*) or serial numbered and lettered circles by alternating between number and letter sets (*Part B*). Because of the contribution of mental flexibility, the test is often used to assess executive functioning. For completeness, it must be mentioned that many complex attention tests also involve executive functions, which will be presented later in a separate point.

### *Perception*

Another topic of interest in high-altitude research is visual or auditory perception, which, obviously, also includes tactile perception and the olfactory sense, but the latter will not be discussed in detail here.

Visual perception tests require little or no physical handling of the test material. However, the complexity of brain functions makes overlap inevitable, and most tests also assess other functions such as attention, spatial orientation, or memory. Testing for unilateral inattention or neglect, the absence of awareness of visual stimuli in the left field of vision, commonly associated with lesions in the right hemisphere, can be done with the *Line Bisection Test* [56], where a patient is asked to bisect a line. The *Judgement of Line Orientation* examines visual estimation abilities for angular relationships between line segments [57, 58].

Auditory perception examines, in part, skills in phoneme discrimination and speech sensation through the *Speech Sounds Perception Test* [59].

### *Memory*

Efficient memory can retain information and use it for adaptive purposes. This requires the intact functioning of many and in some cases especially vulnerable brain regions. In this regard, two subsections are of great interest. The measurement of memorability is examined by three

testing procedures: assessing encoding by immediate retrieval trials and intermediate application of interference during the delay period. Also, in the case of underperformance, the application of other techniques to understand whether the poor performance is a retention or a retrieval problem. A test for the measurement of verbal memory and supraspan is the *Serial Digit Learning Test* [58], another *Auditory Verbal Learning Test* [60, 61]. Tests for visual memory contain the *Continuous Visual Memory Test* [62], visual recall can be assessed by the *Complex Figure Test: Recall Administration* [63-65] and visual memory by *Brief Visual Memory Test-Revised* [66].

Test batteries for memory are displayed by the *Wechsler Memory Scale* [67, 68]. There are furthermore, paired memory tests or memory questionnaires.

### *Verbal functions and language skills*

This heading includes tests for aphasia. Here, spontaneous speech, the ability to repeat words or sentences, syntax comprehension, the power to name things, reading and writing are tested. There are different tests for this, the *Aphasia Screening Test* [69] being one of the most widely used ones. For the examination of naming via confrontation naming, i.e. the calling of shown objects or pictures, for example the *Boston Naming Test* [70] is used, for example.

### *Construction and motor performance*

Next to copying abilities, assessed for instance by the *Benton Visual Retention Test* [71], assembling and building can be investigated in two-dimensional construction by *Block Design* [53, 54, 72].

Neuropsychological Assessment tests of motor skills and manual dexterity functions are for example pegboard tests e.g. *Grooved Pegboard* [73] or the *Finger Tapping Test* [59].

### *Concept formation and reasoning*

This category contains investigations via verbal formats like the *Proverbs Test* [74, 75] and visual formats as *Raven's Progressive Matrices* [76]. Concept formation by sorting and shifting is seen in the *Wisconsin Card Sorting Test* [77].

The large block of reasoning can be studied by means of verbal procedures e.g. *Verbal Reasoning* [78], via visually presented material or otherwise mathematical, i.e., arithmetic reasoning problems.

### *Executive functions*

Another part of interest lies in the executive functions such as planning and decision making. They are the most complex behaviors and as solid cognitive abilities with sufficient accountability necessary to respond appropriately to novel situations. At altitude the assessment of potential dangers is essential for survival. They further form the basis of many skills in the areas of cognition, emotion, and social skills. Willpower, planning and decision-making, goal-directed action, and effective performance are listed as four major components in the concept of executive functions.

A test of self-regulation is the *Verbal Fluency Test* [79], which is also used in association with the *Controlled Oral Word Association Test* [80].

### *Neuropsychological assessment batteries*

A comprehensive examination of cognitive functions by the use of neuropsychological test batteries has two main purposes; on the one hand functional assessment of patients with a proven neurological disease and, on the other hand, diagnostic accuracy. Especially for the latter, tests with good sensitivity and specificity are selected, which also have a sufficient predictive value. A positive predictive value represents the probability that a person has a disease or condition given a positive test result, a negative predictive value the opposite if this is not present.

Next to formalized batteries for use in general clinical practice there are also battery sets developed for specialized purpose. Neuropsychologist's orientation can either be characterized by fixed batteries, or one could choose a more adjustable approach, either through a core set of tests with additional tests selected, dependent on the examination issues, or a fully flexible approach more responsive to the question raised.

One of the best-known batteries, the *Wechsler Adult Intelligence Scale* (current version: WAIS-IV) was developed by David Wechsler, originally for measuring intelligence [53, 54, 67, 68]. The fourth edition contains four index scores, and each test can be applied independently of any other tests in the matrix and measures specific aspects of cognition, some of which have been mentioned previously under the respective cognitive domain.

- *Verbal Comprehension* with the subtests *Similarities*, *Vocabulary*, *Information*, *and Comprehension*
- *Perceptual Reasoning* containing *Block Design*, *Matrix Reasoning*, *Visual Puzzles*, *Picture Completion*, and *Figure Weights*
- *Working Memory* including *Digit Span*, *Arithmetic*, and *Letter-Number Sequencing*

- and *Processing speed* with *Symbol Search*, *Coding*, and *Cancellation*

A screening tool for dementia is the *Mini-Mental State Examination* [81], which has been established as a widely adopted method in clinical practice. It easily and quickly assesses a limited number of cognitive functions, a perfect score being 30 points and the cut-off score being set at 23/24. Factor analyses identified the distinct domains concentration or working memory, language and praxis, orientation, memory, and attention span [82].

The original *Quick Mild Cognitive Impairment Screen* [83, 84] has six subtests namely orientation, registration, clock drawing, delayed recall, verbal fluency, and logical memory and is also available for tablet computer application. The application is occasionally found in the literature on altitude research; however, no study on it was included in this review.

Computer-based batteries in general, are able to assess a wide spectrum of cognitive functions and at the same time have advantages in execution, standardization and data evaluation. The following computer-based batteries are mentioned again later on in the results section. By now, they are commercially organized and in addition fully digitally mapped and adaptable to problem questions.

The *Automated Neuropsychological Assessment Metric* (*ANAM*) was initially programmed for assessing initial effects of concussions [85]. With testing in the domains of attention, concentration, reaction time, memory, processing speed, decision-making, and executive function it contains 23 individual tests.

The *Cambridge Neuropsychological Test Automated Battery* (*CANTAB*) is divided in 23 tests for attention and psychomotor speed, executive function, memory, and social and emotional cognition [86].

The *Computerized Neurocognitive Test Battery CNS Vital Signs* includes tests for *Verbal and Visual Memory*, *Finger Tapping*, *Symbol Digit Coding*, the *Stroop Test*, a test of *Shifting Attention* and the *CPT*. So, within others, it covers mental processes like simple motor performance, attention, memory, and executive functions [87].

The *CogState Computerized Battery* is another commercially organized testing system that holds several tests like *Simple* and *Choice Reaction Time*, or tests to assess working memory and so on [88].

### *Critical view on "the best performance method"*

Besides methods like interviews, historical data, or clinical judgment there is a tremendous count of tests and systematized behavioral observation techniques for evaluating cognitive functions of adults. To complement the theory and practice of neuropsychological assessment, it should be said that the tests listed above virtually all use "the best performance method". The level of best performance serves as the best estimate of premorbid ability and becomes the standard against which all other aspects of the subject's current performance are compared. This method uses test results, mainly numerical, which are usually simpler, less expensive, and more comparable [4]. A fundamental assumption in choosing the best performance method is that not being able to replicate the best result suggests an influence by the factor under study. The difficulty here is to eliminate other influencing factors. At altitude, for example, the study setting alone may have adverse influences. For example, poor performance on a cognitive paper pencil test in a cold ambient temperature, which might also require gloves, is probably not entirely due to cognitive losses caused by hypoxia, but probably also haptic and motoric conditions. The consensus here is that computer-based testing can help standardize testing modalities to allow for better replicability. Another major issue is the influence of practice effects on repeated performance of one and the same test. In this context, it is mainly improvements due to prepared expectations and routine through repetition. The improvement can compensate for deteriorations that might be caused by the factor under investigation. The investigators partly try to compensate this effect, for example, by previous familiarization trials and/or the use of matched control groups. In a review for the symposium "Biomedicine of High Terrestrial Elevations", held at U.S. Army Research Institute of Environmental Medicine in 1967 [89], McFarland notes the challenges of interpreting cognitive performance during high-altitude expeditions as follows [90]:

> *"The subtle influence of hypoxia may often be masked by changes in the learning process or by 'trying harder'."* and *"One of the most difficult problems encountered in measuring performance concerns (...) the learning process.",* as well as *"Motivation is an extremely difficult variable to control."*

## 1.2 High-altitude medicine

The developments in alpine and high-altitude medicine have contributed decisively to the success of mountain sports, enabling to reach new places and altitudes in their approximately 100 years of history. Nevertheless the doctrine in force at the time was occasionally contradicted by

individual alpinists. In the 1960s, first categorical studies on acclimatization to extreme altitudes were conducted and the complex phenomenon of altitude deterioration was elucidated [91].

The following is a brief overview of the subfields of altitude medicine relevant to this thesis.

### 1.2.1 Classification of altitude levels

On mountains there are several factors that can be a hazard to life which are made particularly more dangerous owing to the decrease in oxygen pressure at high altitudes, which exerts a major effect upon human physiology. With a ratio of 20.93 percent of oxygen, the composition of atmosphere in high altitude is the same as at sea level. However, the total atmospheric pressure and therefore oxygen pressure declines exponentially with altitude [92, 93]. While the atmospheric pressure at sea level is 1013.25 hPa or 760 mmHg under normal conditions (0 °C), it averages only 253 mmHg at the summit of Mount Everest (8,848 m), corresponding to 33.3 % of the pressure at sea level [94]. Consequently, when a person is exposed to high altitude, hypobaric hypoxia (HH) is present above a certain threshold altitude. This must be distinguished from normobaric hypoxia (NH), which is achieved by reducing the oxygen concentration in the inhaled air. Figuratively speaking, high-altitude mountaineering consists of a stepladder of subacute, i.e. not sudden, exposures to previously unfamiliar altitudes between sea level and 8,848 m. The human organism reacts with multiple compensation mechanisms to altitude exposure, and a distinction must be made between acute and chronic adaptations. Likewise, a nuanced consideration of different altitude levels must take place, since the physiological compensation mechanisms vary depending on the altitude exposure. The decisive factor for acclimatization is the sleeping altitude, i.e. the altitude at which one spends the night. The organism will already react at a sleeping altitude of about 1,500 m, although these altitudes are usually not perceived as dramatic. If there are no symptoms, one speaks of an instant adjustment. Regarding the reactions of the human organism, the definition of specific, generally valid altitude ranges has so far remained unfulfilled. The transition ranges between altitude levels are up to several hundred meters in altitude and also depend on the weather conditions, the season and the latitude. And not least, the individual in question reacts very differently to the subdivided altitude ranges due to different genetic disposition. The so-called threshold altitude, formerly regarded as central, objective and generally valid altitude range, above which acclimatization is necessary or above which altitude sickness is possible, is obsolete to the knowledge of today. Recent data from genome research have made clear that everyone has personal critical altitudes at which altitude

acclimatization begins as a comprehensive, multi-layered and staggered adaptation process. Unfortunately, the relevant literature still contains different altitude classifications with misleading level designations. Three threshold altitudes are presented below [94].

Medium altitudes 1,500-3,000 m:

Beyond an altitude of about 1,500 m above sea level, performance begins to decline and the minute volume of breathing increases. The arterial oxygen saturation ($S_aO_2$) hardly changes, but the arterial oxygen partial pressure ($p_aO_2$) does. Acute altitude sickness is widespread in the higher altitudes, especially since they are reachable by the large tourist crowds.

High altitudes 3,000-5,500 m:

At these altitudes, permanent acclimatization is possible and thus also a permanent inhabited settlement, wherein a rapid and prominent hypoxemia during exertion and sleep is characteristic. The most severe forms of altitude sickness also known as HAPE and HACE occur primarily from these altitudes onward.

Extreme altitudes 5,500-8,848 m

At these altitudes, hypoxemia, hypocapnia and alkalosis dominate, which is why only a short stay is possible. Due to progressive deterioration of physiological processes, a hitherto possible altitude acclimatization is gradually being eliminated.

For the sake of completeness, the distribution of four altitude ranges by Hultgreen [92] is presented here, classified according to occurrence and severity of medical problems:

(1) moderate (intermediate) altitude: 1,500-2,440 m (5,000-8,000 feet)
(2) high altitude: 2,440-4,270 m (8,000-14,000 feet)
(3) very high altitude: 4,270-5,490 m (14,000-18,000 feet)
(4) extreme altitude: 5,490-8,848 m (18,000-29,028 feet)

Subsequently the first mentioned distribution will be used.

### 1.2.2 Physiological background of altitude adjustment

As the partial pressure in the lungs is crucial for the oxygenation of the blood, a decrease leads to a reduced content of oxygen in arterial blood. Usually raising above an elevation of about 2,500 m is when symptoms of altitude unease begin. The high-altitude symptoms become more severe with increasing altitude, and with faster ascent rates. [92]. During exposure to altitude, the body tries to compensate for its decrease of oxygen in the circulating blood by employing some physiological mechanisms, such as increasing the pulmonary ventilation. Nevertheless, those mechanisms are not endlessly efficient with increasing altitude, resulting in a deficit in the partial pressure of oxygen in blood and tissues as consequence, defined as hypoxia. It refers to an $O_2$ deficiency in the environment or an $O_2$ deficiency in organs or the entire organism. The term hypoxemia represents a reduced $O_2$ saturation of the hemoglobin (Hb) in the blood which, under certain circumstances, can lead to critical tissue hypoxia in borderline organ perfusion. Hypoxemia based on hypobaric or normobaric hypoxia are of particular importance in altitude and sports medicine. Depending on the degree and duration, any form of hypoxia leads to changes in metabolic processes, including energy production at the cellular level [92, 93].

Altitude adjustment is a dynamic process, which can be very different for each individual and is reversible after returning to the lowlands. Acute adaptation to a specific altitude, or altitude acclimatization, is a complex performance of the whole organism with main participation of the cardiovascular and respiratory system with the aim to maintain the oxygen supply. In the following, individual changes of the organism are to be differentiated during exposure to high altitudes.

#### *Respiratory drive*

During acute exposure to high altitude, one of the first compensatory mechanisms is an increase in ventilation. After an acute rapid ascent, this augmentation takes place continuously during the first 10-14 days. An increasing sensitivity of peripheral chemoreceptors to hypoxia is assumed to be the reason for this prolonged effect which eventually leads to an increase in $S_aO_2$ during this period [95]. Under conditions of acute altitude hypoxia, the respiratory drive is triggered primarily by hypoxic stimulation of peripheral chemoreceptors. Those chemoreceptors of the respiratory center in the medulla oblongata react predominantly to arterial or cerebrospinal changes in pH and arterial carbon dioxide partial pressure ($p_aCO_2$) [96]. Both an acute rise

in the $H^+$ ion concentration (acidosis) and an increase in $p_aCO_2$ (hypercapnia) lead to an elevation of the respiratory drive and thus of the respiratory minute volume [97]. Result of the increased ventilation is again a respiratory alkalosis, which, depending on the altitude exposure, can be completely or incompletely compensated by the increased excretion of bicarbonate by the kidneys. While full compensation is still possible at 2,200 m [95], this does not seem to be possible at an altitude of 5,260 m, even after a longer stay [98].

The mechanism of "hypoxic ventilatory response" (HVR), i.e., increased respiratory activity leads to respiratory alkalosis ($p_aCO_2$ decrease, pH increase) and the respiratory center in the core areas of the prolonged medulla is eventually inhibited again. This appears to be possible under both HH and NH conditions, and there is sufficient evidence that even "artificial" hypoxia causes an increase in HVR for hours to days, and this can persist for days to weeks after hypoxia exposure ends [97]. Hypoxemia basically leads to vasodilation and therefore to an increase in cerebral blood flow, except for the pulmonary vessels, which respond with vasoconstriction to hypoxemia. By contrast, hypocapnia leads to vasoconstriction as well as a decrease in cerebral blood flow. In arterial hypoxia, cerebral oxygenation is the result of a balance of hypoxemia and hypocapnia, between vasodilation and vasoconstriction, whereas vasodilation predominates and is discussed to be a plausible explanation for the frequently occurring high-altitude headache [3]. Breathing depth and breathing frequency subsequently settle at a level adapted to the degree of hypoxia or altitude. However, respiratory regulation is subject to numerous influencing factors such as the current hormone status (catecholamines, thyroid hormones, progesterone), body temperature, but also pain, stress, emotions, and pulmonary stretch receptors (Hering-Breuer inflation reflex). Cellular sensors continuously measure the current $p_aO_2$ and alveolar oxygen partial pressure ($p_AO_2$) and initiate a corresponding adaptation of respiratory function via afferent nerve fibers. The increased respiratory drive at altitude results from the decrease of $p_aO_2$, which is mainly registered by oxygen-sensitive cells of peripheral chemoreceptors at the division site of the carotid artery on both sides (carotid body in the carotid fork) and at the aortic arch (aortic glomus). In addition to $p_aO_2$, the carotid bodies also contain sensors for $p_aCO_2$ and pH as well as blood glucose sensors, whose information is also transmitted to the brain in form of afferent nerve signals. Peripheral chemoreceptors in the two carotid bodies can maintain a respiratory drive corresponding to sea level to supply the organism with $O_2$ within a vital threshold range. The sensory fibers emanating from the peripheral chemoreceptors end at the lower edge of the fourth ventricle (Obex) in the solitarius nucleus. These central

afferences to the bulbar respiratory center are essential for adequate HVR and thus for respiratory acclimatization. Peripheral chemoreceptors can influence the respiratory rate and depth in a reflexive way, and to a lesser degree also the heart rate, whereby their sensory impulses are predominantly transmitted via cervical and thoracic pathways of the glossopharyngeal nerve (IX) and vagus nerve (X). The actual sensor cells in the carotid body are so-called type I cells (main cells), which are in close contact with dendrites of the IX cranial nerve (carotid branch of the glossopharyngeal nerve) and react exclusively to a decrease in $p_aO_2$ and not to a decrease in $O_2$ transport capacity, such as in anemia or restriction of the cardiac output [96].

Hypoxia causes a decrease in $p_aO_2$ and consequently also in $S_aO_2$, an effect that can already be observed at altitudes below 1,000 m. The maximal oxygen uptake ($VO_2max$) is also reduced during exposure to altitude. An improvement in $VO_2max$ through regular endurance training is decisive for physical performance at altitude after full acclimatization, but cannot per se rule out the occurrence of AMS or HAPE [96]. Different from what might be expected, $VO_2max$ was found to be more reduced in a competitive athlete collective than in amateur athletes in a study at altitudes of 485 m and 3,000 m [99]. This is most likely because the former already undergo strain-induced arterial hypoxemia on a regular basis in normoxia and therefore are more susceptible to declines in $VO_2max$ compared with normoxemic athletes [100]. Furthermore, hypoxia-induced vasoconstriction in the pulmonary circulation and thus increased pulmonary arterial pressures occur during altitude exposure [101]. A disproportionate increase in pressure is seen as the basis of HAPE; the severity is a matter of strong individual differences [95].

### *Hematology and cardiovascular system*

Under resting conditions, acute exposure to altitude also leads to an increase in heart rate, although the resting heart rate remains slightly elevated even after acclimatization has occurred. With respect to maximum heart rate, a reduction of 1 beat/min per 130 m increase in altitude above 3,100 m has been described *[102]*. An initially increased cardiac output, due to the reduction of stroke volume on the basis of plasma volume reduction, falls back to normoxia values in the course *[103]*. This reduction in plasma volume occurs due to the altitude diuresis briefly mentioned earlier, which leads to a relative increase in Hb concentration [102, 104]. Even at moderate altitude exposure between 1,500 m and 2,000 m, a decrease in plasma volume of up to 300 ml can be observed, with a subsequent increase in Hb concentration reaching up to 1 g/dL. At higher altitude exposure, this process is increasingly amplified. After only a few hours, an increase at the cellular level of the transcription factor hypoxia-inducible factor 1α

(HIF-1α) can be detected, which stimulates the synthesis of the kidney-derived hormone erythropoetin (EPO) and thus erythropoesis. Although EPO levels decrease after about three weeks at altitude, hb concentrations continue to increase during prolonged stays at altitude *[105]*.

#### *Sleep*

Poor sleep or poor sleep quality with increased, at least subjectively perceived, wakeful phases and their influence on reduced physical and mental performance during the day were already described by high-altitude physicians more than 100 years ago. In this context, it was also known that there is no real habituation effect in this connection, but that the sleep quality deteriorates rather linearly to the altitude. In contrast to altitude sickness, symptoms do not persist at the same level above a certain altitude or decrease with progressive acclimatization [36, 106]. In healthy individuals beyond the 4,000 m limit, there are periodic breathing patterns with variations of breathing depth and frequency as well as interposed central apneas (brief respiratory arrests >10 s) frequently observed during night sleep [107]. This nocturnal respiratory periodicity can be seen as a sign of incomplete respiratory adaptation [108]. The disturbed night sleep is primarily a consequence of the imbalance between HVR and the alkalotic braking of the respiratory centre. Especially the reduction of $p_aCO_2$ (hyperventilation-related hypocapnia) with suppression of the respiratory drive should be the critical point of periodic breathing for healthy persons. Even a small increase in $p_aCO_2$ can restore normal breathing (eupnoea) during sleep. In the temporal course of this imbalance, increasing ventilatory acclimatization leads to better sleep quality, since it is based on an increase in ventilation through an elevation of peripheral chemo- and baroreceptor sensitivity as well as a weakening of the inhibitory effect of hypocapnic alkalosis. The greatest decrease in subjective sleep quality and the greatest increase in respiratory periodicity, including arousals, occur during the first nights after arrival at unusually high altitudes [96]. The arousals that involve the termination of apneas are associated with an output of adrenaline, and are therefore made responsible for the sleep disturbances and also tachyarrhythmias [36]. In contrast to native high-altitude dwellers with mitigated hypoxia sensitivity, nocturnal periodic breathing occurs to a large extent in lowlanders with high ventilatory hypoxia sensitivity [96].

### 1.2.3 Medical problems at altitude

In the following, an overview of high-altitude related illness syndromes will be given. Thereafter, further medical topics relevant for this review will be illustrated.

All mountaineers who climb from low altitudes below 900 m to altitudes above 1500 m within a few hours and stay there for days up to weeks can fall ill in the first days after arrival due to altitude, which is associated with the decrease in air pressure and thus oxygen partial pressure with the consequence of oxygen deficiency in the tissue [1]. The first recorded story from China about mountain crossings with physical symptoms we now refer to as acute altitude sickness dates back to about 400 BC and describes manifestations of high-altitude pulmonary edema [109]. Several altitude-induced health problems have now been described, amongst others altitude headache, retinal hemorrhage or peripheral edema due to fluid accumulation in the skin and intermediate connective tissue [36, 110, 111]. In the following, three other, during acute stay at altitude clinically relevant and pathophysiologically different, phenomena are described [112].

- Acute mountain or altitude sickness
- High-altitude cerebral edema, and
- High-altitude pulmonary edema

### *Acute mountain sickness*

AMS is a self-limiting disease whose symptoms occur when mountaineers climb from valley locations to unusual altitudes and remain there for longer than 6-24 hours. After about 36 hours, the symptoms reach their peak and finally disappear from the fifth day on at the same altitude; however, they may reappear during the subsequent ascent. Also, healthy and above all young, efficient mountaineers are affected if they ascend too quickly and with too much exercise intensity regarding their individual performance limits. The concept of a so-called threshold altitude, above which altitude-related illnesses are to be expected, was abandoned because there is a large range of interindividual, geographical and climatic variation. Basically, the occurrence of AMS is to be expected from an altitude range between 1,500 and 3,000 m. AMS includes headache, mostly localised in the forehead or temple area, rarely one-sided or in the back of the head, rather dull and oppressive and significantly intensified by physical exertion as well as bending down or press breathing. If only headache occurs individually, it is referred to as high-altitude headache. About half of those affected develop further symptoms, whereby the term AMS is used if at least one of the following symptoms is also present: loss of appetite, nausea, vomiting, dizziness, drowsiness, lack of drive, listlessness, or general severe malaise. The average altitude gain over several days is regarded as decisive for the occurrence, i.e. a rapid ascent with the same susceptibility often triggers AMS symptoms, while a slow ascent can be

completely asymptomatic [1]. In summary, the most important assessment criteria for susceptibility to AMS are, besides a history of AMS or other altitude-related disease, a genetic predisposition [113, 114], residential altitude, previous altitude exposure or preacclimatization, ascent rate and highest altitude. Whereas the degree of physical training and fitness, age, sex and smoking do not seem to have any influence [1, 115].

### *High-altitude pulmonal edema*

High-altitude pulmonary edema usually occurs after arrival at an altitude above about 3,000 m in the first two to five days. In addition to the frequently accompanying symptoms of AMS, there is often a reduction in performance or exertional dyspnea, cough, and thoracic pressure. If the disease progresses, there may be a heavy cough with whitish to reddish foamy sputum, difficulty breathing, rattling over the lungs, cyanosis, tachypnea, and occasionally fever up to a maximum of 38.5 °C, the so-called alarm symptoms. The oxygen saturation may drop to levels below 50 % and arterial $p_aO_2$ can decrease to 25 mmHg [116]. The saturation can be used in conjunction with anamnesis and clinical examination to make a diagnosis since HAPE typically occurs mainly at great altitudes, thus in an environment without the possibility of classical medical diagnostics [2]. HAPE is also the most common cause of death in acute high-altitude illness, although the mortality rate is lower than in the considerably scarcer HACE [3].

### *High-altitude cerebral edema*

High-altitude cerebral edema is considered to be the most severe form of acute altitude sickness. The pathophysiological mechanisms are still not sufficiently explainable, but the basis of the considerations is the fact that the central nervous system reacts the most sensitively to hypoxia. HACE used to be considered the terminal stage of AMS, but it can develop completely independently, even though it is characterized by the same symptoms as AMS: headache, malaise, and fatigue, which can progress to ataxia, changes in consciousness, hallucinations, coma, and eventually death [3]. Signs further include papilledema, extensor plantar responses, and other neurological signs. It is currently assumed that HACE is both a vasogenic and a cytotoxic edema based on an increased permeability of the blood-brain barrier [117]. It represents a life-threatening acute encephalopathy in the sense of generalized neurological phenomena, with death possibly occurring within a few hours. Moreover, the lethality rate is particularly high for the so-called "combined altitude oedemata" (HAPE plus HACE) [3].

It is noteworthy, however, that the three high-altitude illnesses have only hypobaric hypoxia and respectively hypoxemia as a common causality. Besides this, they share that the incidence

of AMS/HAPE/HACE does not correlate with sex, $VO_2$max, training status, blood pressure, diet, cigarette smoking, or age, whereas statistically it does with the individual HVR as well as with the mountain target and ascent rate. Plus, people who have already suffered from AMS, HACE, or HAPE remain particularly susceptible to it throughout their lives [3].

### *Chronic mountain sickness*

For the sake of completeness, at this point a brief mention of chronical altitude disease will be made. Chronic mountain sickness (CMS) was first described by Carlos Monge in the Peruvian Andes in 1925 and is therefore also known as Monge's disease. The disease is a clinical syndrome that occurs in natives or long-term residents above 2,500 m, by definition, and is characterized by an abnormal increase in erythrocyte count, hematocrit, and Hb concentration (females Hb 19 g/dL; males Hb 21 g/dL) with minimal to moderate arterial hypoxemia [118]. As previously mentioned, exposure to high altitude initially results in a relative increase in Hb concentrations and, with longer duration, eventually in an absolute increase. A higher hematocrit level leads to an increase in blood viscosity and could result in reduced flow in the mucosal capillaries [105]. The increased blood viscosity therefore also causes uneven blood flow through the lungs (ventilation/perfusion mismatch) and thereby hypoxemia despite the high potential oxygen capacity of the blood. The most severe cases of CMS manifest in profound arterial hypoxemia, very high Hb concentration, and, in some cases, moderate or severe pulmonary hypertension that may develop into cor pulmonale leading to heart failure. Typical clinical symptoms include, but are not limited to, headache, dizziness, shortness of breath, sleep disturbances, fatigue, localized cyanosis, poor concentration, and memory impairment. The clinical picture of CMS gradually fades after descent to lower altitudes and reappears after return to higher altitudes [118, 119].

### *Psychiatric problems in altitude*

According to the vulnerability stress model for the pathogenesis of mental diseases, the stress associated with altitude exposure, coupled with the stress caused by physical exertion, lack of sleep, etc., predispose to the occurrence of psychiatric symptoms [111].

A special form of mental status change is evident in the isolated psychosis in very high and extreme altitudes recently systematically analyzed by Hüfner et al. (2018) [120]. It was recognized as a distinct clinical entity, differing from HACE or mental status change from other origins. Psychotic symptoms such as hallucinations, delusions, confused speech, or thoughts can occur without further symptoms of a delirious syndrome at altitude. To give the Third Man

syndrome as an example, where a person feels that somebody is going ahead or behind them and can sometimes see and hear that person, but without anyone actually being there. These symptoms of isolated high altitude induced psychosis disappear when descending to lower areas but are associated with an increased incidence of accidents and near misses. The cause for this can be found in a disturbed reality control under which the individuals concerned cannot correctly assess situations. Persons suffering from symptoms of psychosis must therefore not be left alone or to be given the power to make decisions within the scope of the tour [111]. Episodes of psychosis during high-altitude exposure were reported regularly but were not specifically investigated or attributed to medical diagnoses [120]. Therefore, the pathophysicological meachnisms for isolated psychosis in very high and extreme altitudes are still outstanding.

### 1.2.4 Research methods

#### *Equivalence model of hypobaric hypoxia and normobaric hypoxia*

A hypoxic environment means that the $p_iO_2$ is lower than at sea level, either with lower total air or barometric pressure ($P_B$) in terms of HH, or with correspondingly lower $O_2$ volume fraction ($F_iO_2$) and normal $P_B$, which would be NH. HH ($FiO_2$ = 20.7 %; $P_B$ < 760 mmHg) can be of terrestrial circumstances or generated by lowering $P_B$ in closed systems. NH ($FiO_2$ < 20.7 %; $P_B$ = 760 mmHg) would be "artificial hypoxia" either by $N_2$ enrichment of the respiratory air or via rebreathing systems with $CO_2$ absorption. Artificial $O_2$-deficient conditions, e.g., in NH chambers at normal altitude, attempt to produce hypoxia conditions corresponding to the hypoxia level of a given geographic altitude [92, 93].

Basically, the organism reacts relatively stereotypically to hypoxia regardless of whether HH or NH is present, and both forms lead to an equally reduced $p_iO_2$ < 150 mmHg [121, 122]. Any reduction in $P_B$ or $p_iO_2$ that leads to an equally reduced $F_iO_2$ has the potential to elicit identical physiological responses and functional adaptations [123, 124]. A comparison between simulated normobaric hypoxia and normoxic hypobaria showed that hypobaria per se exerts an influence on the ventilation behaviour due to hypoxic pulmonary vasoconstriction [125, 126]. Consequently, HH and NH would be largely comparable (equivalence model) [127, 128]. In detail, however, there are differences, some of which are still under discussion [129]. As is so often the case, there is also a frequent problem in high-altitude medicine that comparisons based on existing data do not appear to make sense due to different examination methods, but also because of a frequent lack of quality controls [130, 131]. Nevertheless, there is a growing body of evidence demonstrating moderate differences between HH and NH exposure, particularly in

ventilation, fluid balance and nitric oxide (NO) metabolism, but also in the benefit of improved endurance performance and the prevention of AMS [124, 126]. Overall, this crystallizes that HH might be a more severe environmental condition compared to NH and also leads to different physiological adaptations [124]. It therefore seems reasonable to assume that the equivalence model only stands for an approximate isohypoxia of HH and NH since $P_B$ in particular is likely to have an independent effect on hypoxia and AMS [126]. In this regard, the effectiveness of HH exposure in terms of sustainable pre-acclimatization may also be somewhat more pronounced than that of NH atmosphere since HH is intended to simulate more precisely the hypoxia stress at natural levels on the entire organism [132]. In either circumstance, the slope of the oxygen transport cascading from the atmosphere to the mitochondria is reduced, and the effects that result primarily from lower $p_aO_2$ and reduced $S_aO_2$ entail numerous physiological consequences [133]. In this context, the exact nature of the response is influenced by the size of the stimulus of the hypoxic environments: whereas altitudes up to approximately 2,000-2,500 m lie in the flat part of the sigmoidal oxyhemoglobin dissociation curve, higher altitudes lie in the steep part of the curve and therefore require greater adaptation [134].

### *Altitude simulation vs. natural altitude atmosphere*

However, there are also conflicting opinions on altitude simulation, for example, those that hypoxia chambers represented only imprecise models of a natural altitude atmosphere. It could be assumed that much more complex, interconnected physiological changes would be triggered than it would be the case if only the $P_B$ or $F_iO_2$ were reduced. Some say that in principle there are no major differences between NH and HH [129]. On the other hand, the differences between terrestrial hypobaric and normobaric hypoxia in a simulated altitude environment are far from being fathomed in all directions, especially since atmospheric/climatic conditions in reality are often more complex than experimental conditions in a protected chamber atmosphere at normal altitude could ever be. In recent years, there have been innovations in chamber research, for example, it is now possible to simulate climatic conditions up to extreme values in some highly specialized research locations. This combines pressure chamber technology with environmental simulation methods. It is hoped that this will enable researchers to study the effects of extreme climates on the object under investigation in a controllable environment; longer observation periods are also possible. One climate chamber, for example, is the terraXcube, a center for extreme climate simulation of Eurac Research in Bolzano (South Tyrol/Italy) [135].

In the further course of this review, a distinction will be made not only between HH and NH, but also between nomobaric hypoxia chambers (NHC) and the induction of hypoxia by breathing of hypoxic gas mixture (BHG). In the literature, the latter two are often taken as corresponding to each other. This is, however, not the case, and a separate consideration should be considered reasonable. First, the induction of hypoxia by BHG is abrupt without or with few hypoxic substages and often shorter in time. Moreover, the psychological aspects of wearing face masks are different from those in hypoxia chambers, where there is at least the possibility to move inside the room without restrictions. Further worth mentioning are the usually longer duration of intervention in chambers and the possibility of gradual adjustment of hypoxia.

## 1.3 Cognitive performance at high altitude

### 1.3.1 Oxygen dependence of the brain

The brain demands a steady supply of oxygen to maintain the high rate of ATP production necessary to remain in an electrically active state [136]. When brain activity is enhanced, e.g., by performing a cognitively demanding task, the metabolic demand of neural tissue increases [137]. A decrease in oxygen saturation, like it as occurs during terrestrial high-altitude exposure, can therefore adversely affect brain function and cause a decrease in cognitive performance [13, 138]. Hypoxia and subsequently hypoxemia show in multiple effects on cognitive and physiological functions such as headaches, nausea, and dizziness [8]. Moreover, impaired vision can occur and these changes in visual function, including narrowing of the visual field, blurred vision, and color vision changes, are well documented [139, 140]. The effects of hypoxia may even include the induction of acoustic and visual hallucinations [42], with case reports of triggered sensations of depersonalization and out-of-body experiences. Transient neurological symptoms occur abruptly at more extreme altitudes, often after strenuous exertion, without apparent altitude-induced prodromes. These symptoms are likely to be caused by intense neuronal discharge, neuronal synchronization as a characteristic of epileptic discharge, or cortical expansion of depression [141]. The alterations in emotional processes, sensorimotor abilities, and especially thinking skills therefore result in overarching impairments in mood, performance, and intellectual functioning [142-144].

### 1.3.2 Brief history and current state of research

It is generally acknowledged that there is a negative correlation between altitude and cognitive performance [145] and the beginnings of cognitive altitude studies date back to the 1920s and 1930s. Among others, these were conducted by the early pioneer in examining the impact of

high altitude on decline of cognitive performance, Ross Armstrong McFarland. Even then, hypoxia experiments were performed using the Douglas bag technique or in chambers, both pressure chambers and oxygen-deficient chambers [146].

As already mentioned, a hazard while moving in terrain at risk of falling is the exercise of risky behavior. Making quick and correct decisions can be essential for survival when you consider the inhospitable and sometimes life-threatening environment at high altitude. While the ability of accurate reasoning and quick decision making is an advantage at sea level, at high altitudes nonrationally made decisions can potentially lead to falls or accidents and in the worst case to exhaustion and death [147, 148]. Previous consecutive experimental studies have shown an increase in risky decision making in hypoxic conditions compared to normoxic conditions [149, 150]. Since the influences of cognitive function manifest themselves behaviorally, neurobehavioral tests are considered a sensitive and valid method for the detection of cognitive dysfunction [151, 152]. Additionally, subtle changes in cognition might be hard to assess and some of the commonly used written tests are just too insensitive. To access those slight changes computerized neuropsychological testing batteries have been developed and actually found to be sensitive enough to detect mild impairments. They are helpful developments for high-altitude testing as they can be handled easily and seem to have good psychometric features for repeated testing [89, 153].

In the last years there have been some published reviews in relation to topics of interest:

By comparing six studies in a review with meta-analysis, Urrunaga-Pastor and colleagues (2021) [154] found the occurence of cognitive impairment and dementia being nearly double among older adults living at high altitude compared to other regions of the world.

A narrative review by Ando and colleagues (2020) [41] examined the effects of acute exercise and hypoxia on cognitive performance. They concluded that the effects of acute physical exercise on cognitive performance appear to depend on the intensity and duration of exercise and that moderate exercise has positive effects. They further propose that the combined effects of acute exercise and hypoxia on cognitive performance are mainly determined by the interaction between exercise intensity and duration, the severity of hypoxia, and the duration of hypoxia exposure. The physiological mechanisms of interaction, that is, when acute training is combined with hypoxia, are thought to be changes in neurotransmitter function, cerebral blood flow, and possibly cerebral metabolism.

In terms of publications relevant to this review on effects of altitude on cognition, there are also noteworthy articles. As the exact findings of previous research will be dealt with in the further course of this work, we will limit ourselves here to a rough overview of the most important insights.

One of the older articles by Virués-Ortega, Buela-Casal, Garrido, and Alcázar (2004) [155] presents a review regarding the effects of moderate, high, and extreme altitude on neuropsychological functioning. Prolongation of reaction time and changes in accuracy and motor speed were noted, the latter already at lower altitudes. Impairments in codification and short-term memory had been observed mainly at altitudes above 6,000 m. Furthermore, deficits in verbal fluency, speech production, cognitive fluency and metamemory were noted. They also summarized decreased tactile, olfactory, pain and taste thresholds as well as somesthetic illusions and visual hallucinations.

A work by Petrassi, Hodkinson, Walters, and Gaydos (2012) [156] examined hypoxic impairments with respect to aviation-related tasks at moderate altitude such as mental functions as well as sensory deficits. The results of this study revealed deficits in learning, reaction time, decision making, and certain types of memory, although the authors note that the results appear inconsistent and difficult to replicate. The literature on hypoxic visual deterioration, on the other hand, was found to be more consistent and demonstrated such impairment.

Taylor, Watkins, Marshall, Dascombe, and Foster (2016) [145] collected research for a focused review about temperature like heat stress and cold stress as well as the impact of hypoxia on cognitive function. The accumulated evidence suggested that the effects of hypoxia on cognitive function depend on both task and severity. Moreover, performance on both simple and complex tasks appeared vulnerable, and this was the case even at moderate altitudes.

McMorris, Hale, Barwood, Costello, and Corbet (2017) [157] even carried out calculations on 22 experiments for a systematic meta-regression analysis of the effects on central executive and non-executive tasks. They found low $p_aO_2$ (35-60 mmHg) to be the main predictor of cognitive performance decline. Interestingly, the effect proved to be independent of whether the exposure was conducted under hypobaric or normobaric hypoxic conditions. Contrary to their expectation, no significant differences were found between central executive and non-executive, such as perception/attention and short-term memory, tasks.

A very detailed systematic review by Martin and colleagues (2019) [24] examined various environmental stressors such as heat, cold, and hypoxic stress on cognitive performance. In contrast to this work, they also included studies that investigated military task performance. In terms of summarizing the studies and effects of hypoxia on cognitive performance, they came to a very heterogeneous picture. However, they concluded that it was the severity and duration of the stay at altitude that had the greatest influence on cognition, rather than complexity of the tasks. Furthermore, they saw a large influence factor in the interindividual variation and recommended to include individual factors and their responses in future studies. Another point was that altitude acclimatization seems to have a positive effect on cognitive performance, but an optimal protocol is still pending.

### 1.3.3 Critical view upon the state of research

One problem of the published studies examining cognitive performance under hypoxia and at altitude is the largely heterogeneous methods and techniques used to reach the conclusions. The vast diversity of tests available to researchers, together with the inherent variability of the tests, may be one reason why there is a debate in the literature as to whether cognitive degradation occurs at certain altitudes [6, 144, 153, 158, 159]. The difficulties associated with field expeditions and the numerous differences to controlled environmental chamber studies also do not contribute to the consistency of the results [89]. Not to mention the differences in duration and severity of hypoxia and exposure with or without prior acclimatization [8]. Furthermore, in most cases, for reasons of feasibility of mountaineering expeditions or due to limited space in high-altitude chambers, the number of participants examined is restricted to a very small number of cases. The test persons of the individual studies range from normal persons to high end climbers, so when individual physiological differences are taken into account, intra subject variability introduces additional complications, and these subsequently lead to inconclusive results [8, 89].

Referring to the current state of research, this is the first systematic review that attempts to summarize all the evidence for and against cognitive impairment across moderate and high altitudes, explicitly listing the neuropsychological tests used and addressing their sensitivity at the altitudes studied.

# 2. Materials and methods

## 2.1 Literature search on high-altitude effects on cognitive performance

A systematic literature review examining cognitive function and potential hypoxic deficits at high altitude was performed, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [160].

### 2.1.1 Search strategy and study selection

A comprehensive systematic literature search was performed in the PubMed electronic database through October 2021. The search string in "all fields" was as follows: "altitude", "normobaric hypoxia" or "hypobaric hypoxia" combined with "cognition", "cognitive", "neuropsychological" or "test". First, all returned titles were screened to exclude duplicate studies. After screening of title and abstract studies, the selected studies were read carefully to identify those appropriate for inclusion. Articles found in the literature search were manually checked for any citations to relevant articles not listed in the electronic databases.

### 2.1.2 Inclusion and exclusion criteria

The PICOS approach (patients, intervention, comparator, outcomes, and study design) came to use to specify inclusion and exclusion criteria.

The inclusion criteria were studies with: (1) healthy adult subjects exposed to an altitude equal or above 2,440 m (either actual or through generated conditions corresponding to the intended altitude); (2) Cognitive function assessment in the context of altitude exposure using an experimental design; and (3) within-subject design with a control condition, where the baseline test condition may at most be measured up to 1,500 m; or between-subjects design with a matched control group tested under normoxia.

Excluded were: (1) studies with first test time point one month or longer after arrival at altitude and studies with subjects exposed to chronic hypoxia such as miners for the possibility of drawing conclusions from direct effects of altitude; (2) studies that explicitly examined the effect of altitude by modulating another variable such as sleep deprivation, exercise, or the intake of pharmaceutical agents; (3) studies performing only electrophysiological cognitive measures (e.g., event related potentials); (4) studies conducted with professional pilots or military personnel; and (5) case reports, reviews, expert opinions, comments, or letters to the editor, studies on animals, conference or abstract reports and articles not written in English.

The primary search provided the following: 1404 articles, 21 abstracts, 14 Reviews, 2 Meta-analyses. An additional 30 sources were gathered from inspecting the references with the original search criteria. As a whole 52 articles were included. On two occasions there are two articles ([161, 162] and [163, 164]) with each referring to the same study but presenting different tests, which is why all four are listed in the following. The excluded articles and their reasons for being ruled out are listed under the Chapter Supplemental material. Figure 2-1 shows an overview of the inclusion process via flow diagram.

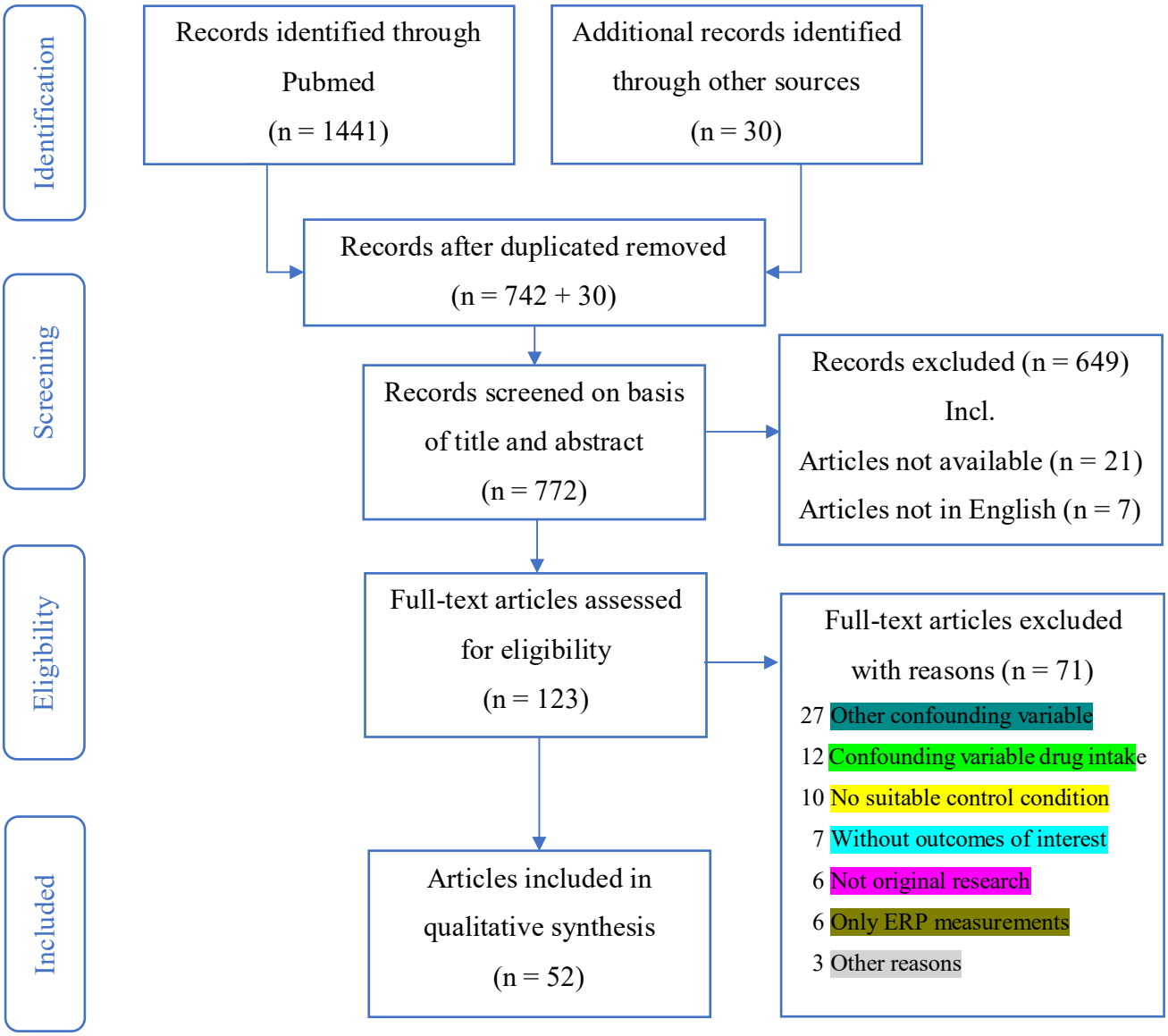


**Figure 2-1 Flow diagram of article selection**

## 2.2 Data extraction and management

The publications with demographic and experimental data were screened for several factors like field or chamber study, hypobaric or normobaric hypoxia intervention, ascent profile, use of the STAR core parameters [165], and subject information. The following data were extracted from each included study: number, sex and mean age of participants, study protocol with experimental condition, when given, ascent rate, and duration of altitude exposure, timing and duration of neuropsychological test administration, neuropsychological test type and the related cognitive domains, and significant results indicating changes in cognitive performance. The effects of altitude on cognitive performance found in the studies is presented below in simplified form; the presentation was done in the style of the review by Martin et al. (2019) [24] mentioned earlier, as it was perceived to be very well arranged.

## 2.3 Quality assessment via STAR data reporting guidelines for clinical high-altitude research

The STAR data reporting guidelines were used to evaluate the study quality. The consideration of the core parameters was considered positive, which is why a higher number would be understood in principle as better study quality of the articles. The aim of the STAR (Strengthening Altitude Research) initiative [165] was to create a standardized collection of core elements for research and reporting in clinical altitude medicine, see Table 2-1. The inventory consisting of consensus-based guidelines was developed under application of the Delphi method and a group of experts in the field of clinical high-altitude medicine with the aim of improving data reporting by means of a uniform data reporting protocol and consequently enhancing the quality of scientific evidence. The core parameters selected with an expert consensus of more than 80 % should, according to the authors' views, be obligatory for research proposals and high-altitude reports. Those core parameters consist of five sections respectively SETTING, INDIVIDUAL FACTORS, AMS & HACE, HAPE, and TREATMENT, with 42 subcategories in total. Moreover, 47 additional parameters also reached consensus on a second, open list of parameters that depend on specific research questions and whose reporting is not mandatory for every research project concerning SETTING, INDIVIDUAL FACTORS, SYMPTOMS, SIGNS, SCORES, ADDITIONAL EXAMS, IMAGING, and THERAPY. The core parameters should help to objectivize the research reports and thus also support the comparability, and finally, the reproducibility of study results, especially about the often, challenging study conditions.

**Table 2-1 STAR data reporting guidelines [165]**

| Section | Parameters |
|---|---|
| Section 1: SETTING (n=6) | 1.1 Study location |
| | 1.2 Setting |
| | 1.3 Altitude |
| | 1.4 Starting point of the ascent |
| | 1.5 Maximum altitude reached |
| | 1.6 Mode of ascent (active or passive) |
| Section 2: INDIVIDUAL FACTORS (n=10) | 2.1 Age |
| | 2.2 Sex |
| | 2.3 Pre-existing altitude exposure |
| | 2.4 High-altitude native |
| | 2.5 Pre-existing health conditions |
| | 2.6 History of prior AMS |
| | 2.7 History of prior HACE |
| | 2.8 History of prior HAPE |
| | 2.9 Pre-acclimatization |
| | 2.10 Altitude of residence |
| Section 3: AMS & HACE (n=11) | 3.1 Headache |
| | 3.2 Gastro-intestinal symptoms |
| | 3.3 Fatique / weakness |
| | 3.4 Dizziness / light-headedness |
| | 3.5 Ataxia |
| | 3.6 Change in mental status |
| | 3.7 AVPU |
| | 3.8 $S_pO_2$ |
| | 3.9 Time of fulfilling AMS definition – this suggests time of onset, not diagnosis |
| | 3.10 Time of fulfilling HACE definition – same, needs to be consistent with text |
| | 3.11 New Lake Louise AMS Score |
| Section 4: HAPE (n=11) | 4.1 Weakness / decreased exercise performance |
| | 4.2 Dyspnea at rest |
| | 4.3 Cough |
| | 4.4 Tachypnea |
| | 4.5 Orthopnea |
| | 4.6 Pink frothy sputum |
| | 4.7 Respiratory Rate |
| | 4.8 Heart Rate |
| | 4.9 $S_pO_2$ |
| | 4.10 Rales and wheezing |
| | 4.11 Time of fulfilling HAPE definition – as above |
| Section 5: TREATMENT (n=4) | 5.1 List all drugs with generic names, dosages, mode of administration, dosage intervals and indication |
| | 5.2 Supplemental oxygen |
| | 5.3 Hyperbaric bag |
| | 5.4 Descent |

## 2.4 Classification of the used neuropsychological test types into supercategories

The neuropsychological test procedures were grouped into supercategories on the basis of the cognitive domain studied. A large part of the information about which cognitive domain is supposed to be examined by the test was given directly in the body text of the studies. In addition, other sources such as Lezak [4] were consulted for classification. In the presence of different classifications in Lezak's standard work and the study itself, Lezak was preferred. It should be noted that individual tests often require the interaction of several cognitive domains. For example, in a test to determine a subject's reaction time, a motor response is usually expected, e.g., by pressing a button when a signal occurs. A test will only be listed under its primary cognitive domain. In the example mentioned, for instance, the test will only be listed under reaction time instead of additionally psychomotor function. It should be noted that this forced simplification by drawing an artificial dividing line is, of course, a potential source of error.

# 3. Results

One main purpose of this review was the classification of the used neuropsychological tests and their aptitude for detecting impairment of cognitive performance, if existing. The tests and their dedication to various cognitive domains have been defined previously [4].

## 3.1 Quantitative description of the research methods

In terms of the study protocol of all 52 experiments performed, 29 studies were conducted in the field, with 31 articles* being published about them. 23 studies took place as laboratory studies, including two studies that investigated both conditions** [166, 167]. In eight of the field studies there was only passive ascent to altitude. Of the laboratory studies, seven were performed establishing NH via inhalation of gas mixture, eleven took place in NHC, and in five of the studies it was possible to access a hypobaric hypoxia chamber (HHC). Regarding the field investigations, the experimental study sites were located at altitude meters between 2,590 m [168] and 7,200 m [147], with the highest point reached also at 8,848 m [169]. Among the laboratory studies, the oxygen conditions studied ranged from corresponding altitudes of 2,440 meters above sea level [170] to a maximum of 8,848 m [171], see also Table 3-1. Studies were published between 1963 and 2021.

**Table 3-1 Study classification according to type of operation**

| | |
|---|---|
| Field studies (n = 29) | |
| Passive ascent only (n = 8) | Davranche et al. (2016) [8] |
| | Frost et al. (2021) [172] |
| | Gibbons et al. (2020) [173] |
| | Latshang et al. (2013) [168] |
| | Pun, Guadagni et al. (2018)*[1] [161] |
| | & Pun, Hartmann et al. (2018)*[1] [162] |
| | Roach et al. (2014)*[2] [163] |
| | & Subudhi et al. (2014)*[2] [164] |
| | Schlaepfer, Bärtsch, and Fisch (1992)** [167] |
| | Shi et al. (2016) [174] |
| Passive and active ascent (n = 21) | Bjursten et al. (2010) [7] |
| | Bonnon, Noël-Jorand, and Therme (1999) [175] |
| | Dykiert et al. (2010) [176] |
| | Falla et al. (2021) [177] |
| | Griva et al. (2017) [178] |
| | Harris, Cleland, Collie, and McCrory (2009) [153] |
| | Issa et al. (2016) [89] |
| | Karinen and Tuomisto (2017) [169] |

| | |
|---|---|
| | Kramer, Coyne, and Strayer (1993) [158]<br>Lefferts et al. (2019) [179]<br>Lefferts et al. (2020) [180]<br>Limmer, Platen (2018)* [166]<br>Malle, Ginon, and Bourrilhon (2016) [147]<br>Merz et al. (2013) [181]<br>Nelson et al (1990) [182]<br>Pelamatti, Pascotto, and Semenza (2003) [183]<br>Petiet, Townes, Brooks, and Kramer (1988) [184]<br>Phillips, Griswold, and Pace (1963) [185]<br>Phillips and Pace (1966) [186]<br>Weigle et al. (2007) [187]<br>Zhang et al. (2013) [188] |
| Laboratory studies (n = 23) | |
| Breathing of hypoxic gas mixture (n = 7) | Altbäcker et al. (2019) [189]<br>Chroboczek, Kostrzewa, Micielska, Grzywacz, and Laskowski (2021) [190]<br>Kourtidou-Papadeli et al. (2008) [170]<br>Loprinzi et al. (2019) [191]<br>Ochi et al. (2018) [192]<br>Schlaepfer, Bärtsch, and Fisch (1992)* [167]<br>Stepanek et al. (2013) [193] |
| Chamber study (n = 16) | |
| Normobaric hypoxia (n = 11) | De Aquino Lemos et al. (2012) [194]<br>Limmer and Platen (2018)* [166]<br>Niedermeier et al. (2017) [195]<br>Parker, Manley, Shand, O'Hara, and Mellor (2017) [196]<br>Pighin, Bonini, Hadjichristidis, Schena, and Savadori (2019) [149]<br>Pighin et al. (2012) [150]<br>Pramsohler et al. (2017) [197]<br>Seo et al. (2015) [198]<br>Seo et al. (2017) [199]<br>Turner, Barker-Collo, Connell, and Gant (2015) [200]<br>Williams et al. (2019) [201] |
| Hypobaric hypoxia (n = 5) | Abraini, Bouquet, Joulia, Nicolas, and Kriem (1998) [171]<br>Asmaro, Mayall, and Ferguson (2013) [6]<br>De Bels et al. (2019) [202]<br>Nakano et al. (2015) [203]<br>Pavlicek et al. (2005) [204] |
| Legend<br>*[n] Same study with two articles<br>** Investigation of both conditions | |

## 3.2 Qualitative review of the collected studies

In Table 3-2 an overview of the analyzed studies and their findings of altitude impact on cognitive performance is shown, and the analyzed data of all studies are presented in a standardized way. Facts of interest were the study participants with number, sex and age, the study protocol with temporal duration, type of intervention, altitude profile as well as information on the control group/examination, the numbers of the STAR core parameters if considered in the study, the temporal and situational use of the neuropsychological tests, the neuropsychological tests with their higher-order cognitive domain, and finally the results of the study. For a better overview, only the first author and the year of publication are given in addition to the numerical source citation. The arrow symbols represent the results of subsequently mentioned tests with ↔ meaning no effects, unchanged performance, ↑ standing for increased or better performance and ↓ for reduced or worse performance.

The use of familiarization sessions/test trials before the start of the actual cognitive assessments has been mentioned in several articles, which has been included in the tables. These familiarization trials are supposed to minimize learning effects or practice effects in the intrasubject comparisons. To take these learning effects over the course of several tests into account, control groups were involved in eight articles [153, 158, 161, 166, 171, 175, 178, 195]. Learning effects were also discussed or considered in another 32 articles. In three articles, extensive familiarization trials were used to try to establish a performance plateau in advance [8, 170, 179]. In Lefferts (2019), moreover, additional training sessions occurred during the field study "*to prevent loss of task familiarity owing to the passage of time between test days*" [179]. Another method has been the use of parallel versions or alternative forms of the applied tests, which are mentioned in 17 articles [6, 7, 153, 161, 164, 169, 170, 172, 177, 178, 181, 182, 184, 195, 198-200] and will be marked in the following by $x^1$ (meaning alternate forms used). Among them test batteries in nine articles: the *Computerized Neurocognitive Test Battery CNS Vital Signs* [7, 200], the *CogState Computerized Battery* [153], the *Cognition Test Battery* [172], the *PC based Multiple Attribute Task Battery* [170], the *FACTRETRIEVAL2 Test Battery* [182], the *Cambridge Neuropsychological Test Automated Battery* [161], the *ANAM -4th Edition* [198, 199], and the *Defense Automated Neurobehavioral Assessment Test Battery* [164].

## Table 3-2 List of articles and their findings of altitude impact on cognitive performance

| First authors | Number of participants (sex)/Mean age of participants (Mean ± SD); profession if mentioned | Study protocol: Time of exposure, experimental condition, altitude profile, maximum altitude reached (Mode of ascent – active/passive) - Study protocol baseline or control group (CG), altitude (test event if named) | STAR core parameters | Timing of neuropsychological test administration under exposure (test event if named)/Duration of Test Battery | Test Battery: Neuropsychological tests (*Cognitive Domain*) + Further investigations that are not part of this review | Changes in cognitive performance ↔ ↑ ↓ based on significant results, $p < 0.05$ (test event if named) |
|---|---|---|---|---|---|---|
| Abraini (1998) [171] | 8 (M)/26.5 (range 24–37) y; climbers<br><br>Control group (CG) 8 (M)/24.5 (range 22–40) y | 31-days, hypobaric chamber, sea level (SL) to 8,848 m above sea level (ASL)<br>-<br>6-days pre-acclimatization at 4,350 m (passive); 3x Pre baseline cognitive assessment (BCA) and 1x Post cognitive assessment (CA), each at SL<br><br>CG at SL | Section 1<br>2.1-2.3<br>2.9<br>Section 3<br>4.8, 4.9 | 7 assessments over 31 days between 4,500 m and 8,848 m/Not available (NA) | Pegboard-Psychomotor Test (*Psychomotor ability*)<br>Number Ordination Rey's Test (*Mental efficacy - reasoning*)<br>Visual Choice Reaction Time (*reaction time*) | <u>Pegboard-Psychomotor Test</u><br>↓ At 8,000 m (compared to CG), at 8,848 m and post exposure (compared to BCA)<br><u>Number Ordination</u><br>↑ Until 6,500 m (compared to BCA)<br>↓ At 8,000, 8,848 m and post exposure (compared to CG)<br>↔ <u>Visual Choice Reaction Time</u> |
| Altbäcker (2019) [189] | 12 (2 F)/32.72 (range 28–39) y; recreational climbers | 43 min, breathing of hypoxic gas mixture via oronasal breathing mask equivalent to 5,500 m of altitude<br>-<br>Pre BCA under normoxia, Post CA | 1.1-1.3<br>1.5<br>2.1-2.5<br>2.9, 2.10 | After 23 min of hypoxic gas exposure/20 min | Modified CPT (*attention*)<br>Number-Size Stroop Variant Task (*executive function*)<br>+<br>EEG recordings and ERP data analysis | <u>CPT</u><br>↔ Overall performance<br><u>Stroop Task</u><br>↔ Overall performance<br>↑ Efficiency for congruent and neutral stimuli |
| Asmaro (2013) [6] | 35 (4 F)/NA (range 19-69 y); aviation industry employees | 35 min, hypobaric chamber, 5 min at 7,620 m ≙ 25,000 ft following 30 min at 5,334 m ≙ 17,500 ft with intermittent breathing of $O_2$<br>-<br>Pre BCA and Post CA, altitude NA | 1.1-1.5<br>2.1-2.3<br>3.6<br>5.2 | 3 assessments after entering chamber at 7,620 m ≙ 25,000 ft/5 min and two tests at 5,334 m ≙ 17,500 ft starting at the first and second half of the 30-min exposure/NA | Word-Color Stroop Task[1] (*executive function*)<br>Digit Span Forward Task[1] (DST-F) (*short term memory*)<br>DS Backward Task[1] (DST-B) (*working memory*)<br>Trailmaking A Task[1] (*attention*)<br>Trailmaking B Task[1] (*executive function*) | <u>Stroop Task</u><br>↓ Correct trials<br>↑ Faster reaction times at 7,620 m<br><u>DST-F</u> at 7,620 m & <u>DST-B</u> at 5,334 & 7,620 m<br>↓ Correct responses<br><u>Trailmaking A and B Task</u><br>↓ Slower completion times at 5,334 & 7,620 m |

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| Bjursten (2010) [7] | 7 (NA)/NA (range 42-51 y); physicians (≥5 y of alpine experience) | 5 days, field study, 1,115 m (NA) to 3,000 m (passive) to 4,554 m (active)<br>-<br>Pre-study: one night at 2,864 m (passive)<br>Familiarization session, Pre BCA and Post CA at 1,115 m | Section 1<br>2.1, 2.2, 2.6, 2.9, 2.10<br>Section 3<br>4.8, 4.9 | 3 assessments at 3,647 m (2), 4,554 m (3) and again at 3,647 m (4)/25 min | CNS Vital Signs[1]:<br>Verbal Memory Test (*memory*),<br>Visual Memory Test (*memory*),<br>Finger Tapping Test (psychomotor speed),<br>DSST (reaction time),<br>Word-Color Stroop Test (executive function),<br>Shifting Attention Test (executive function) | ↔ Verbal and Visual Memory Test, Finger Tapping Test, DSST, Word-Color Stroop Test and Shifting Attention Test<br><br>Negative correlations of the Lake Louise Scale & calculated cognitive domains<br>memory at 3,647 m (2)<br>Reaction time at 4,554 & 3,647 m (3 & 4)<br>Processing speed at 4,554 & 3,647 m (3 & 4) |
| Bonnon (1999) [175] | 7 (3 F)/NA; occasional alpinists | 30 days, field study, 3,500 m (passive) to 6,200 m (active)<br>-<br>BCA at 300 m (A1)<br>CG under normoxia | Section 1<br>2.1-2.3<br>Section 3<br>5.4 | 2 CAs day 2 at 3,500 m (A2),<br>day 17 at 5,400 m (A3)/NA | Cognitive Motor Task with Pocket Calculator (*Short term memory*)<br>+<br>Semidirected and subject-centered interview about mood states | ↔ Cognitive Motor Task compared to CG |
| Chroboczek (2021) [190] | 15 (M)/23.1 ± 2.1 y; physically active | 30 min, breathing of hypoxic gas mixture via face mask equivalent to 3,500 m ≙ $F_iO_2$ 13 %<br>-<br>Familiarization session, CA under normoxia, altitude NA | 1.1-1.3<br>2.1-2.3<br>2.5 | One assessment after 30 min of acute exposure/NA | Stroop Interference Test (*executive function*)<br>Stage 1. giving "names" of colors<br>Stage 2. "reading" color names<br>Stage 3. giving the name of the font color, each word is written with | ↓ Slower time and time delta of stage 3 naming interference values |
| Davranche (2016) [8] | 11 (M)/28 ± 8 y; regular recreational climbers | 4 days, field study, 4,350 m ≙ 14,272 ft (passive)<br>-<br>Familiarization session, CA at SL | Section 1<br>2.1, 2.2, 2.5, 2.6<br>Section 3<br>4.8 | 3 assessments on the day of arrival (D0), the second day (D2) and fourth day (D4) | Simon Task (*excecutive function*)<br>Time Perception Task (*spatiotemporal Integration*) | Simon Task<br>↓ Slower reaction times (D0)<br>↓ Decision errors twice as high over time of altitude exposure with the congruent trials<br>↔ Decision errors with the incongruent trials<br>↓ Time Perception Task<br>Underestimating of durations |
| De Aquino Lemos (2012) [194] | 10 (M)/24.9 ± 5.02 y | 24 h, normobaric chamber, 433 mmHg ≙ 4,500 m ASL ≙ $F_iO_2$13,5 %<br>-<br>BCA at normoxic conditions, altitude NA | 1.1-1.3<br>2.1-2.3<br>2.5<br>3.1, 3.2 | One Assessment 24 hours after the start of exposure to hypoxia/NA | DST-F (*short term memory*)<br>DST-B (*executive function*)<br>Sequences of Numbers and Letters (*working memory*)<br>Corsi Blocks Forward (*short term memory*) and Backward (*working memory*)<br>Random Number Generation (*working memory*)<br>Stroop Color and Word Test (*attention*) | ↓ DST<br>Lower sum of the ranks, sum of direct order, sum of order, and span of direct order<br>↓ Sequence of Numbers and Letters Test<br>Lower number of correct answers<br>↓ Corsi Block Tests<br>Lower values for direct order, inverse order, sum of orders, and span of order inverse |

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| | | | | | + Polysomnography, EEG, Brunel Mood Scale questionnaire | ↓ Random Number Generator Test Higher index indicating worsening ↓ Stroop Color Test Changes varying in expression over the three test stages with higher completion time, less correct answers and more errors |
| De Bels (2019) [202] | 17 (M)/26.3 ± 8.1 y | 4 h with ascent and descent, exposure time "on the top" 3 h 20 min, hypobaric chamber, reproduction of a cable car ride scheme and stay at a mountain top, 3,842 m - Pre-ascent BCA and Post-descent CA at SL | 1.1-1.3 2.1, 2.2, 2.4, 2.5 4.8, 4.9 | One assessment after at least 1 h of exposure/NA | PEBL: Modified Math Processing Task (*Arithmetic Reasoning Problems*), Perceptual Vigilance Task (*reaction time*), Time Wall Estimation Task (*spatiotemporal integration*) + Critical flicker fusion frequency | ↔ No change in performance in all three tests |
| Dykiert (2010) [176] | 10 (4 F)/21.5 ± 1.4 (range 19-24) y | 20 days, field study, from 1,992 m to 3,271 m (passive) then with 1.5 m/min up to 5,565 m (active) ASL - 4 x CA at 76 – 86 m ASL prior to expedition | Section 1 2.1, 2.2, 2.3 Section 3 4.8 | 21 assessments, approx. daily/NA | Four-choice RT (*attention*) | ↓ Four-choice RT Increased reaction times above 4,000 m revealed in linear mixed modeling |
| Falla (2021) [177] | 36 (18 F)/ 27.3 ± 4.1 (range 22–40) y; health care personnel | 3 days, field study, From 1,258 m to 2,178 m (passive) then in 3:30 h to 3,269 m (active) - Familiarization session, BCA at 1,258 m (D1 S1) | Section 1 2.1-2.3 2.5-2.10 Section 3 4.8 | 3 assessments: upon arrival at 3,269 m (D1 S2), morning of the second day (D2 S3) morning of the third day (D3 S4)/NA | DSST[1] (*attention*) PVT[1] (*reaction time*) Balloon Analogue Risk Task (BART) (*risky decision making*) + Hospital anxiety and depression scale, State Trait Anxiety Inventory, Pittsburgh Sleep Quality Index, Insomnia Severity Index, Perceived Stress Scale, Wagnild and Young's scale | DSST ↓ Number of correct responses (processing speed) (D2 S3), ↔ Back to normal (D3 S4) PVT ↔ Mean reaction time, number of lapses and number of false starts ↓ Higher number of false starts with higher Insomnia Severity Index BART ↑ Faster total time (D3 S4), ↑ Mean earnings (D3 S4) ↔ Number of pumps |

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| Frost (2021) [172] | 15 (5 F)/M 24.9 ± 4.3 y; F 26.4 ± 5.1 y (M+F range 19-32 y) | 3 days, field study<br>340 m to 1216 m in 4 h and from 1,216 m to 3,800 m in 2 h (passive)<br>-<br>Some assessments had practice sessions, Group split in half with either pre-ascent BCA or post-descent CA at 340 m ASL | Section 1<br>2.1-2.3<br>2.5<br>Section 3<br>4.8 | Testing on three consecutive days at 3,800 m (ALT1, ALT2, ALT3)/30 min | Cognition by Joggle Research[1]:<br>PVT (*reaction time*)<br>BART (*risky decision making*)<br>DSST (*attention*)<br>Line Orientation Task (visuospatial analytic ability)<br>N-Back Task (executive function)<br>Visual Object Learning Task (*Visual memory*)<br>Abstract Matching (Visuospatial analytic ability)<br>Motor Praxis Task (*psychomotor ability*)<br>+<br>Nocturnal actigraphy and polygraphy, Pittsburgh Sleep Quality Index, Stanford Sleepiness Scale, PROMIS Sleep Disturbance questionnaire | ↓ PVT<br>Slower reaction times (ALT3)<br>BART<br>↑ Faster reaction times (ALT2 + ALT3)<br>↔ Number of pumps<br>↔ DSST, Line Orientation Task, N-Back Task, Abstract Matching, Motor Praxis Task |
| Gibbons (2020) [173] | 10 (M)/27 ± 11 y | 16 ± 4 days, field study, from SL in 6 h to 4,330 m (passive)<br>-<br>Familiarization test, BCA at 344 m prior to expedition | Section 1<br>2.1, 2.2, 2.5<br>4.7-4.9 | One assessment after 16 ± 4 days/~3 min | Pro-point and Anti-Point Tasks (*executive function*) | ↔ No change in performance |
| Griva (2017) [178] | 198 (60 % M)/44.5 ± 13.7 y;<br>CG: 25 (60 % M)/44.5 ± 14.1 y | 11 days, field study, from 3,500 m up to 5,300 m (active)<br>-<br>BCA at 75 m ASL prior to expedition<br>CG at/or near SL, NA | Section 1<br>2.1-2.3<br>2.5<br>Section 3<br>4.8, 4.9 | 3 assessments with CA on either day 1 or day 2 after arrival at: 3,500 m, at 5,300 m on day 11, at 1,300 m on return | Trail Making Test Parts A[1] (*attention*) and B[1] (*executive function*)<br>Controlled Oral Word Association Test[1] (*executive function*)<br>Letter Cancellation Test (*attention*)<br>Stroop Test (*executive function*)<br>Grooved Pegboard (*psychomotor ability)*<br>Rey Auditory Verbal Learning Test (*verbal memory*)<br>Symbol Digit Modalities Test[1] (*attention*)<br>Block Design Test (*assembling and building*)<br>+ | ↓ Attention, verbal abilities and executive functioning<br>↓ Memory and psychomotor function<br>↑ Cognitive decline greater amongst older people<br>↓ Cognitive function after descent |

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| | | | | | Brief Center for Epidemiologic Studies Depression Scale, State Trait Anxiety Inventory | |
| Harris (2009) [153] | 26 (11 F)/M 34.9 (range 23-53) y; F 32.5 (range 25-40) y;<br><br>CG: 411 (32 F)/M 34.2 (range 25-55) y, F 34.2 (range 25-40) y | 18 days, field study, from 410 m up to 5,400 m (active)<br>-<br>Practice test, CA at SL prior to expedition<br><br>CG, NA | Section 1<br>2.1-2.3 | One assessment within the first 24 hours of arrival at 5,100 m/NA | DST-F[1] (*short term memory*)<br>DST-B[1] (*working memory*)<br>DSST[1] (*attention*)<br>Trail-making Test, Part B[1] (*executive function*)<br>Rey's Auditory-Verbal Learning Test[1] (*verbal memory*)<br>Controlled Oral Word Association Test[1] (*executive function*)<br>CogState[1]:<br>Simple Reaction Time (*reaction time*)<br>Choice Reaction Time (*executive function*)<br>Monitoring Task Reaction Time (*attention*)<br>Monitoring Task Accuracy (*attention*)<br>Working Memory Task Reaction Time (*attention*)<br>Working Memory Task Accuracy (*working memory*),<br>Learning Task Accuracy (*visual memory*) | ↓ DST-F<br>↑ DSST<br>↑ Trail-Making Test, Part B<br>↑ CogState Monitoring Test improved reaction time<br><br>Performance was more variable in the written than the computerized tests |
| Issa (2016) [89] | 8 (NA)/35 ± 10 y | 23 days, field study, 1,400 m up to 5,500 m (active)<br>-<br>Familiarization trial, Pre-ascent BCA (Baseline) and post-descent CA (Post) at 1,400 m<br>Retesting after return to USA | Section 1<br>2.1, 2.3<br>Section 3 | 3 assessments at 5,500 m on day 2 (T1), day 5 (T2) and day 7 (T3) after arrival at base camp/NA | Rapid Cognitive Assessment Tool (*executive function*)<br>Stroop Color-Word test (*attention*)<br>Trail Making test part A (*attention*) and B (*executive function*)<br>+<br>Profile of Mood States self-report questionnaire, Spielberger State-Trait Anxiety Inventory, Acceptance and Action Questionnaire-II | No calculations of significance but trend to improvement regarding baseline and base camp<br>↔ No significant differences between scores taken at base camp (T1, T2, T3) and the post expedition scores (Post) for all 3 tests.<br>Stroop test performance worsening associated with increase in AMS |

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| Karinen (2017) [169] | 9 (M)/37.6 ± 5.5 (range 27–45) y; experienced climbers | 80 days, field study, 1,400 m to 8,848 m (active)<br>-<br>Pre-ascent BCA (d2) and post-descent CA (d69) at 1,400 m | Section 1<br>2.1-2.3<br>2.10 | 4 assessments each at 5,300 m;<br>the first 2 days after arrival at base camp (d16), then 2 days after setting up camp 3 at 7100 m (d34), the third after 4 days' rest (d43) and 4 days after successful summiting (d62) | Colorado Perceptual Speed Test[1] (*attention*)<br>Number Comparison Test[1] (*executive function*) | ↑ Colorado Perceptual Speed Test<br>Improving speed results during the expedition<br>↔ Number Comparison Test |
| Kourtidou-Papadeli (2008) [170] | Group II: 10 (M+F; NA)/32.1 ± 6,74 y; some are private pilots | NA, breathing of hypoxic gas mixture via face mask equivalent to 2,440 m ≙ 8,000 ft<br>-<br>BCA under normoxia with two-week training to establish a personal performance plateau, post exposure CA under 100 % $O_2$ | 1.1-1.3<br>2.1, 2.2, 2.5<br>4.7-4.9 | Time of hypoxia exposure NA/16 min | MATB – a PC based Multiple Attribute Task Battery[1] (*executive function*)<br>multitask flight simulation package with monitoring, tracking, communications, and fuel management tasks<br>+<br>EEG measurements | ↓ Decrease in performance with statistically significant increase of Root mean scare error compared to normoxic and hyperoxic condition |
| Kramer (1993) [158] | 20 (2 F)/31.2 ± 5.2 y, APTS climbers; 32.3 ± 4.6, category search climbers<br><br>CG: 20 (2 F)/29.3 ± 4.8 y, APTS control; 30.9 ± 3.8 y category search control | Range from 18 to 26 days, field study, from 2,195 m up to NA (active)<br>-<br>Pre-ascent BCA and post-descent CA at 92 m<br><br>CG, NA | Section 1<br>2.1, 2.2<br>3.1-3.6 | Testing altitudes NA/NA | 1st group + CG: Automated Performance Test System (APTS) battery:<br>Pattern Comparison Task (*visuospatial analytic ability*),<br>Code (Letter Number) Substitution Task (*attention*)<br>Choice Reaction Time Task (*executive function*)<br>Memory Search Task (*short term memory*)<br>Finger-Tapping Task (*psychomotor ability*)<br>2nd group + CG: Category Search Task (*efficacy, reasoning*)<br>Consistently Mapped<br>Varied Mapping | ↓ Slow performance with higher reaction and response times<br>↔ No improvement in performance compared to CG<br><br>Learning effects and outcome ↑ in the Consistently Mapped Task than in the Varied Mapping Task<br>↓ Levels of transfer compared to control |

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| Latshang (2013) [168] | 51 (M)/24 (quartiles 20-28) y | 4 days, field study, from 490 m up to 1,630 m and 2,590 m (passive)<br>four groups with block designed altitude exposure<br>-<br>Pre-ascent BCA and Post-descent CA at 490 m | Section 1<br>2.1-2.3<br>2.5, 2.6<br>Sections 3 & 4 | 4 assessments, 2x after night at 1,630 m an 2x at 2,590 m in randomized order/NA | PVT (*reaction time*)<br>Divided Attention Steering Simulator (*attention*)<br>1-, 2-, and 3-Number Back Task (*executive function*)<br>Trail Making Test A (*attention*) | ↔ No change in performance detected |
| Lefferts (2019) [179] | 18 (8 F)/ M 32 ± 15 y; F 20 ± 1 y; (M + F range 18–60) y | 11 days, field study, 1,400 m up to 5,160 m (active)<br>-<br>Extensive familiarization process prior to the trek, and practice tests throughout the trek (hope of practice effects plateau);<br>CA prior to expedition at 116 m ASL | Section 1<br>2.1, 2.2, 2.5<br>Section 3<br>4.7, 4.8 | 3 assessments:<br>day 4 at 3,440 m, day 8 at 4,240 m; and day 11 at 5,160 m/NA | Flanker Task (attention)<br>2-Back version of an N-Back Number Task (executive function) | <u>Flanker Task</u><br>↔ Accuracy<br>↑ Faster RT at 4,240 m<br><u>N-Back Task</u><br>↓ Decreased accuracy at 5,160 m<br>↑ Faster RT for 2-back at all altitudes<br>↓ Modest reductions in caution and non-decision time<br>↑ Bias and strength of evidence for non-match items during the 2-back |
| Lefferts (2020) [180] | 8 (4 F)/23–7 (range 18–41) y | 7-days, field study, 1,400 m up to 4,240 m (active)<br>-<br>BCA on day 0 at 1,400 m altitude | Section 1<br>2.1, 2.2, 2.5<br>Section 3<br>4.7, 4.8 | 2 assessments: day 3 at 3,440 and day 7 at 4,240 m/3 min | Stroop Task (*Executive function*) | ↑ Accuracy at 4,240 m<br>↑ Faster reaction times at 3,440 m and 4,240 m |
| Limmer (2018) [166] | 80 (29 F)/M 25.5 ± 6.0 y; F 24.8 ± 5.9 y<br><br>4 groups<br><u>HYP + EX (hypoxia + exercise)</u>: 15 (3 F)/ M 27.3 ± 11.6 y, F 32.7 ± 17.6 y;<br><u>HYP</u>: 25 (6 F)/M 24.7 ± 3.1 y, F 22.7 ± 2.3 y; | <u>HYP + EX:</u> 7-days, field study, starting altitude NA up to 5,739 m (active)<br>-<br>CA prior to expedition at 154 m (D1) and post-descent CA at 812 m (D18)<br><br><u>HYP:</u> 2x21 minutes, normobaric chamber, 3,500 m ≙ $F_IO_2$ 13,5 % $O_2$ (D14) and 5,800 m ≙ $F_IO_2$ 10.0 % (D16)<br>-<br>Pre- (D1) and post-CA (D18) at 53 m normoxic conditions<br><br><u>NOR:</u> CG at normoxia | Section 1<br>2.1, 2.2, 2.5<br>Section 3 | 2 assessments on days 14 and 16:<br>HYP + EX: day 4 of expedition at 3,995 m (D14), day 6 of expedition at 5,739 m (D16)/6 min<br><br>HYP: day 14 after 15 min of exposure to hypoxia corresponding to 3,500 m (D14), day | Frankfurt Attention Inventory-2 (*attention*)<br>Performance Value, Continuity Value and Quality Value | HYP + EX:<br>↓ Attentional functions in Performance Value and Continuity Value at 5,739 m<br>↔ Quality Value<br><br>HYP:<br>↓ Attentional functions in Performance Value, Continuity Value and Quality Value at 5,800 m |

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|---|---|---|---|---|---|---|
| | NOR-normoxia: 21 (10 F)/M 24.7 ± 3.1 y, F 24.4 ± 2.2 y; EX: 21 (10 F)/M 24.4 ± 1.3 y, F 24.0 ± 2.3 y; | EX: CG with 7-days physical exercise at normoxia | | 16 after 15 min corresponding to 5,800 m (D16)/6 min | | |
| Loprinzi (2019) [191] | 21 (11 F)/21.0 (range 18-35) y | 30 min, breathing of hypoxic gas mixture via face mask $F_iO_2$ = 12 % ≙ 4,000 m ASL - Approx. 24 h apart counterbalanced blinded condition with one control CA under normoxia | 1.1-1.3 2.1-2.3, 2.5, 2.10 Section 3 | After 30 min of exposure start of memory task assessment, after 20 min rest distraction assessment of delayed memory recall/NA | Memory Interference Task (AB/AC paradigm) (*working memory*) immediate and delayed proactive and retroactive interference | ↔ Proactive interference ↑ Retroactive interference for both the immediate and delayed memory assessments, suggesting a reduced memory interference effect ≙ enhanced brain function |
| Malle (2016) [147] | 4 (M)/29.2 ± 1.6 y; professional climbers | 6-weeks, field study, from approx. 1,400 m start with 13-days preacclimatization trek up to 5,500 m, followed by a 4-week progressive ascent up to 8043 m (active) - Familiarization trial, 8-days (BL) prior to expedition and 4- (D61) and 46-days (D103) post expedition CA respectively at 1,050 m | Section 1 2.1-2.3 2.9 Section 3 4.8 | 14 assessments of PASAT between 1,400 m (D1) and 7,200 m (D40)/NA 6 assessments of DST subtests between 1,400 m (D1) and 5,600 m (D35)/NA | Paced auditory serial addition test (PASAT) (*attention*) DST-F (*short term memory*) and DST-B (*working memory*) | ↔ No significant differences in any of the three cognitive tasks |
| Merz (2013) [181] | 32 (7 F)/43 (range 25–62) y; experienced non-professional mountaineers | 21-days until summit reach, field study, mean ascent rate 191-201 m/d, from 3,750 m up to 7,546 m (active) - Familiarization trial, Prior to (ZH1) and 3-months post-expedition CA (ZH2) at 440 m | Section 1 2.1, 2.2 Section 3 4.8 | 3 assessments: 4,497 m (BC), 5,533 m (C1), and at 6,265 m (C2)/NA | Saccadic Eye Movement (*Ocular motor performance*) Line Bisection Test (*visual perception*) Ruff 2/7 Cancellation Test – Letter and Number Condition[1] (*attention*) Ruff Figural Fluency Test (RFFT) (*executive function*) Modified Pegboard, Chess test (*Psychomotor ability*) | ↔ Eye movement experiments revealed no differences in either saccade latency or main sequence ↔ No impairments or dependence on any altitude-related parameter |
| Nakano (2015) [203] | 7 (1 F)/NA (range 19–46 y); climbers | 4 h 15 min, hypobaric chamber, barometric pressure decreases -2 mmHg/min ≙ ascent speed 33 m/min with maintained altitude conditions of 2,000 m, 3,000 m, 4,000 m, and 4,500 m for 30 min | 1.1-1.5 2.1-2.3 4.8-4.9 | One assessment at 4,500 m ASL/NA | Mini-Mental State Examination (*concentration or working memory, language and praxis, orientation, memory, attention span, and other cognitive factors*) | ↔ Normal score of 29.3 ± 0.8. |

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| | | - No control condition, CA as widely adopted method with cut-off score set at 23/24 | | | | |
| Nelson (1990) [182] | 12 (3 F)/NA; climbers | Duration NA, field test, from 1,200 m up to 8,848 m (active) - Pre-ascent (1) and approx. 1-week post-descent BCA (6) at 1,200 m | Section 1 2.2, 2.3 | 4 assessments: after 48 hrs at 5,400 m (2); 2 week trek to 6,500 m, after 48 hrs (3); approx. 2 weeks later at 6,500 m or 7,100 m (4); and at 5,400 m after having reaching ones highest point during this expedition (5)/NA | Modified version of the FACTRETRIEVAL2 test battery[1] (*long-term memory*) Feeling of Knowing (*confidence-judgement*) | ↔ FACTRETRIEVAL2 test battery No reliable changes in mean percent or latency of correct recall, no changes in mean percent correct recognition on nonrecalled items across the five testing locations ↓ Feeling of Knowing declined reliably between the first two tests and the last three tests, the decrease is still present more than a week later |
| Niedermeier (2017) [195] | 22 (11 F)/25.8 ± 5.5 y CG: 20 (8 F)/24.8 ± 4.6 y | 12 h, normobaric chamber $F_iO_2$ = 12.6 % ≙ 4500 m after short-term pre-acclimatization using intermittent hypoxia 7 × 1 h $F_iO_2$ 12.6 % (without physical activity) - Familiarization session CG with sham pre-acclimatization 7 × 1 h at $F_iO_2$ = 20.9 % ≙ 600 m ASL | 1.1-1.5 2.1-2.3 Section 3 4.8 | 4 data collection points after 2, 5, 8, and 10 h in hypoxia/NA | Computer-based Game of Dice Task[1] (*Risky decision making*) | ↓ Adverse risk behavior at 4,500 m But reduced risk behavior in preacclimatized subjects compared to CG Positive time effect on decision making: independent of the group effect, the number of risky decisions decreased over time in hypoxia after controlling for the covariate age. |
| Ochi (2018) [192] | 21 (7 F)/20.5 ± 2.5 (range 18–29) y | 16,5 min, breathing of hypoxic gas mixture via face mask $F_iO_2$ = 16,5 (mild)/13,5 (moderate)/10,5 (severe) % ≙ 2,000/3,500/5,000 m ASL Two practice sessions, CA at SL | 1.1-1.3 2.1, 2.2 4.7-4.9 | 2 d with 2 conditions per day in randomized order, >48 h between first and second day; assessment after 10-min exposure/6,5 min | Color–Word Stroop Task (*executive function*) | ↓ Slower reaction times at 5,000 m ↔ Error rate Significant main effect of condition for reaction time in Stroop interference Negative correlation between reaction time in Stroop interference and $SpO_2$ |
| Parker (2017) [196] | 10 (3 F)/NA; orthopedic surgeons | 45 min, normobaric environmental chamber, $F_iO_2$ = 14.1 % ≙ 3,000 m ≙ 10,000 ft ASL - Practice trial before VWMC, BCA before entering the chamber; | 1.1-1.4 2.2 4.7-4.9 | After 15 min of exposure first VWMC assessment/4-10 min; then surgical skill/maximum of 15 | Operational Span protocol - Verbal Working Memory Capacity (VWMC) with counting span, operation span, and reading span (*working memory*) Surgical Skills by application of an orthopedic external fixator (*psychomotor ability*) | ↔ VWMC Surgical Skills ↔ Completion time ↓ Worse application with higher pin-divergence score as a measure of frame asymmetry |

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| | | Double blind, repeated CA under normobaric normoxia $F_iO_2 = 20.9$ % near SL ≈ 113 m | | min; then again VWMC assessment | | |
| Pavlicek (2005) [204] | 21 (M)/24.2 ± 2.4 y<br><br>AP1/AP2/CP group with 7 subjects each | 2 h, hypobaric chamber,<br>• Altitude profile 1 (AP1):<br>450 (TS1); 1,500 (TS2); 4,500 (TS3) m<br>• Altitude profile 2 (AP2):<br>450 (TS1); 1,500 (TS2); 3,000 (TS3) m<br>-<br>• Control profile (CP):<br>450 (TS1); 650 (TS2); 650 (TS3) m with 200 m "pseudo-ascent" to mask for altitude | 1.1-1.5<br>2.1-2.3<br>4.8, 4.9 | three 30-min test sessions (TSs) separated by 10-min intervals for pressure adjustment/30 min, Letter fluency test 2 min; word association task 1 min | 4 Word-Generation Fluency Tasks - one Verbal Letter Fluency Task and three Category Fluency Tasks (*executive function*)<br>Lateralized Tachistoscopic Lexical Decision Task with high and low emotional target words (*affective flexibility*) | ↔ No significant differences in word fluency, word association, or lateralized lexical decision performances |
| Pelamatti (2003) [183] | 15 (NA)/34.5 (range 29-37) y; mountaineers | 3-5 days, field study, 400 m/day, up to an altitude between 4,500 m-5,050 m during different expeditions (active)<br>-<br>Pre-BCA, twice 15- and 40-days Post-CAs | 1.5, 1.6<br>2.1 | Assessment at 4,500 m respectively 5,050 m/NA | Verbal Free Recall: proper vs. common names (*short-term memory*) | ↓ Recall of proper names<br>↓ Primacy effect<br>↔ Recency effect |
| Petiet (1988) [184] | 8 (F)/33.8 ± 3.8 (range 29-40) y; climbers | 40-days, field study, maximum altitude ranged from 17,300 ft ≙ 5,273 m to 20,500 ft ≙ 6,248 m (active)<br>-<br>CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m<br>Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure | Section 1<br>2.1, 2.2, 2.6-2.8<br>5.1 | 3 assessments:<br>Day 13 at 12,000 ft. ≙ 3,658 m;<br>Day 17 at 14,800 ft. ≙ 4,511 m;<br>Day 31.4 ± 12 (range 30-41 d) at highest elevation ranging from 5,273- 6,348 m/NA | Gorham's Proverbs (*Concept formation*)<br>PASAT (*attention*)<br>DST (*short term memory*)<br>Finger Tapping (*psychomotor ability*)<br>Selective Auditory Attention Task (*attention*)<br>Selective Reminding Test (*verbal memory*)<br>Benton Line Orientation Task (*visuospatial analytic ability*)<br>Boston Naming Test[1] (*Speech production and syntax comprehension*)<br>+<br>Self-perception inventory of cognitive and affective functioning; the Acceptance of Others Scale, Multiple Affect Adjective | ↑ PASAT, also improved post expedition<br><br>↓ Expressive language ability, measured by the Boston Naming Test |

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| | | | | | Checklist-Revised, Environmental Symptoms Questionnaire | |
| Phillips (1963) [185] | Experiment I: 5 (M)/range 18-20 y<br><br>Experiment II: 8 (M)/range 18-20 y | Experiment I:<br>3 days, field study, up to 12,470 ft ≙ 3,800 m ≙ 490 mm Hg (NA)<br>-<br>15-days familiarization with tests 300 ft ≙ 91 m ≙ 752 mm Hg<br><br>Experiment II:<br>2 days, field study up to 14,250 ft ≙ 4,340 m ≙ 455 mm Hg<br>-<br>Two groups, counterbalanced BCA at SL | 1.1-1.3<br>2.1, 2.2<br>4.7, 4.8 | Experiment I:<br>3 assessment days at 3,800 m/Rhymes and Numbers tests max. 60 sec each<br><br>Experiment II:<br>2 assessment days at 4,340 m | DST-F (*short term memory*)<br>Word Span Forward (*short term memory*)<br>Robinson's Rhymes and Numbers tests (*mental efficacy, reasoning*) | Experiment I at 3,800 m<br>↔ No changes<br><br>Experiment II at 4,340 m<br>↓ Rhymes Test<br>↑ Numbers Test |
| Phillips (1966) [186] | 18 (M)/NA | 2-days, field study, up to 3,800 m (NA)<br>-<br>Two groups, counterbalanced BCA at SL | 1.1-1.3<br>2.2, 2.3<br>4.7, 4.8 | 2 assessment days at 3,800 m/distraction task 30 sec | Word Span Forward - immediate and short-term recall<br>with or without 30 sec distraction task of backward subtraction (*short term memory*) | ↔ No significant changes in altitude<br>Only tendency for recall impairment with retention loss: forgetting more items at the end of a list |
| Pighin (2019) [149] | 26 (14 F)/23.3 ± 6.8 y | Exact duration NA, normobaric chamber, $F_iO_2$ = 14.1 % ≙ 3,000 m ASL<br>-<br>Familiarization session, CA under normoxia $F_iO_2$ = 20.9 % ≙ 0 m ASL in randomized order with experimental session | 1.1-1.3<br>2.1, 2.2<br>4.8, 4.9 | After 20 min of exposure/NA | BART (*Risky decision making*) | BART<br>↓ Adverse risk-taking behaviour, higher number of pumps |
| Pighin (2012) [150] | 30 (16 F)/M 23.3 ± 4 y, F 20.5 ± 1.9 y | 70 minutes, normobaric chamber, $F_iO_2$ = 14.1 % ≙ 3,000 m ASL<br>-<br>Familiarization session, CA under normoxia $F_iO_2$ = 20.9 % ≙ 0 m ASL in randomized order with experimental session | 1.1-1.3<br>2.1, 2.2<br>4.8, 4.9 | After 25 min of exposure/45 min | Computer-based Psychomotor Speed Task (*psychomotor ability*)<br>Risk-Taking Task (*Risky decision making*) | ↓ Psychomotor Speed Task<br>8,85 % slower reaction times<br>Risk-Taking Task<br>↓ Adverse risk-taking behaviour for choices involving losses<br>↔ Risk taking behaviour for choices involving gains |

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| Pramsohler (2017) [197] | 11 (5 F)/21 ± 2.1 y | Two separate nights, normobaric chamber<br>1st night $F_iO_2$ = 14,29 % ≙ 3,500 m ASL<br>2nd night $F_iO_2$ = 11,05 % ≙ 5,500 m<br>-<br>BCA at 450 m ≙ $F_iO_2$ = 20.93 % | 1.1-1.5<br>2.1-2.3<br>Section 3 | 2 assessments directly after awakening;<br>mean individual sleep duration:<br>1st night 7,5 h<br>2nd night 3,23 h/10 min | Choice reaction test (Schuhfried) (*executive function*)<br>+<br>Polysomnography | ↓ Slower cognitive reaction times at 3,500 m and 5,500 m<br>→ Positive correlation (r = 0,78) with $SpO_2$; lower $SpO_2$ surprisingly correlated significantly with shorter cognitive reaction<br>↔ Motoric reaction time |
| Pun, Guadagni (2018) [161]<br><br>*(also see Pun, Hartmann (2018) [162])* | 21 (13 F)/25.3 ± 3.8 y<br><br>CG: 17 (12 F)/24.9 ± 2.6 y) | 2 x 6-days field study, Cycle 1: day exposition to 5,050 m, sleeping height 2,900 m (passive);<br>Week of rest at 520 m; Cycle 2: re-exposition following identical schedule<br>-<br>Familiarization trial,<br>2x BCA and post-expedition CA at 502 m<br>CG at 1,103 m | Section 1<br>2.1, 2.2, 2.4<br>Section 3 | 2 assessments each cycle: acute day 1 (Cycle 1 HA1, Cycle 2 HA1), acclimatization day 6 (Cycle 1 HA6, Cycle 2 HA6)/30 min | CANTAB[1]:<br>Reaction Time Task (*reaction time*),<br>Attention Switching Task (*attention*),<br>Rapid Visual Processing (*attention*)<br>One Touch Stockings of Cambridge Task (*executive function*) | ↑ Selective and sustained attention improves with acclimatization<br><br>↔ Improvement gained in cognitive functions during the acclimatization period in Cycle 1 did not carry over to the repeated exposure in Cycle 2 |
| Pun, Hartmann (2018) [162]<br><br>*(also see Pun, Guadagni (2018) [161])* | 21 (13 F)/25.3 ± 3.8 y | 2 x 6-days field study, Cycle 1: day exposition to 5,050 m, sleeping height 2,900 m (passive);<br>Week of rest at 520 m; Cycle 2: re-exposition following identical schedule<br>-<br>Familiarization trial,<br>2x BCA and post-expedition CA at 502 m | Section 1<br>2.1, 2.2, 2.4<br>Section 3 | 2 assessments each cycle: acute day 1 (Cycle 1 HA1, Cycle 2 HA1), acclimatization day 6 (Cycle 1 HA6, Cycle 2 HA6)/10 min | PVT (*reaction speed*)<br>Trail Making Tests A & B (*attention & executive function*)<br>+<br>Actigraphy for Sleep Monitoring, Environmental Symptom Questionnaire, Handgrip strength | <u>PVT</u><br>↓ Slower reaction times at acute exposure to 5,050 m<br>↔ Reaction speed recovers after 6 days at altitude and prevents impairments during subsequent altitude re-exposure<br><u>Trail Making Tests</u><br>↔ reaction times<br>↑ further HA stay leads to improvement |
| Roach (2014) [163]<br><br>*(also see Subudhi (2014) [164])* | 21 (9 F)/20.8 (range 19–23) y | 16-days, field study, from 1,525 m in 3 h with supplemental oxygen up to 5,260 m (passive), after first assessment down to 3800 m for 4-days, then back up to 5,260 m<br>-<br>30-days pior to (SL) and 3 months post-expedition CA at SL | Section 1<br>2.1, 2.2<br>5.2 | 2 assessments:<br>Day 1 after arrival (ALT1) and day 16 (ALT16) at 5,260 m /NA, DANA 20 min | 2x Simple Reaction Time (SRT) Test before (SRT1) and after (SRT2) completion of a 20-min DANA Test Battery;<br>Change score dSRT = SRT1 minus SRT2 (*attention / mental fatigue)* | ↓ Marked decrease in throughput <u>dSRT</u> with acute altitude exposure<br>↔ <u>dSRT</u> normalized with acclimatization |

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| Schlaepfer (1992) [167] | 10 (4 F)/23.8 ± 1.2 y | 25 min,<br>1. field study, from 540 m in <10 min up to 3,450 m (passive)<br>2. Breathing of hypoxic gas mixture via face mask $F_iO_2$ = 14.5 % ≙ 3,450 m<br>-<br>Familiarization trial, BCA at 540 m | Section 1<br>2.1, 2.2<br>2.10 | Respective assessments within 15 min after exposure/10 min | Time Needed Reading Briefly Displayed Letters (*Visual perception*) | ↑ Faster completion time in both hypoxic conditions |
| Seo (2015) [198] | 16 (M)/24 ± 4 y | 2 h, normobaric chamber, $F_iO_2$ = 12.5 % ≙ 4,300 m ≙ 14,110 ft ASL<br>-<br>Familiarization trial and BCA during rest in normoxia<br>+<br>Further examination but not part of this review: CA under low and moderate exercise performance | 1.1-1.3<br>2.1-2.3, 2.5<br>4.8, 4.9 | One assessment after 60-min at rest/5 min | ANAM -4th Edition subtests[1]:<br>Go/No-Go Test (*response inhibition*)<br>Running Memory Continuous Performance Test (RMCPT) (*working memory*) | ↔ Go/No-Go Test no statistical differences<br>↓ RMCPT less % correct and throughput score impaired compared with rest in normoxia |
| Seo (2017) [199] | 15 (F)/22 ± 2 y | 2 h, normobaric chamber, $F_iO_2$ = 12.5 % ≙ 4,300 m ≙ 14,110 ft ASL<br>-<br>Familiarization trial and BCA during rest in normoxia $F_iO_2$ = 21 %<br>+<br>Further examination but not part of this review: CA under low and moderate exercise performance | 1.1-1.3<br>2.1-2.3, 2.5<br>4.8, 4.9 | Two assessments after 30- and after 60-min at rest/5 min | ANAM-4th Edition[1]:<br>RMCPT (*working memory*)<br>Total Mood Disturbance (*affective flexibility*) | ↔ RMCPT no change after 30- or 60-min rest in hypoxia<br><br>↓ Total Mood Disturbance score worse after 30- and after 60-min rest in hypoxia compared to baseline |
| Shi (2016) [174] | 30 (M)/25.2 ± 1.9 y | 3 h, field study, up to 4,280 m (passive)<br><br>Retrograde calculated division into AMS and non-AMS group<br>-<br>BCA "in the plain", altitude NA | Section 1<br>2.1-2.3<br>2.10<br>Section 3<br>4.8 | One assessment after 3h of exposure/NA | Visual-DST (V-DST) (*short term memory*)<br>Auditory-DST (A-DST) (*short term memory*)<br>Paced Visual Serial Addition Test (PVSAT) (*attention*)<br>PASAT (*attention*)<br>Picture Recall Test (*short term memory*)<br>Picture Recognition Test (*short term memory*) | ↓ A-DST, PVSAT, PASAT, and Picture Recognition Test<br>↔ V-DST and Picture Recall Test<br><br>AMS vs. non-AMS group:<br>↓ V-DST, A-DST, PVSAT, PASAT, and Picture Recognition Test scores<br>↔ Picture Recall Test scores not different between groups |

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| Stepanek (2013) [193] | 25 (11 F)/32.4 ± 9.8 y | 5 min, Breathing of hypoxic gas mixture via face mask $F_iO_2$ = 8 % ≙ partial pressure 24.3 mmHg ≙ 23,300 ft ≙ 7,101 m<br>-<br>Familiarization tests, BCA and 3-min post CA at normoxia | 1.2, 1.3<br>2.1, 2.2, 2.5<br>Section 3 | One assessment after 3 min exposure/<2 min | King-Devick Test (*ocular motor performance*) | ↓ 18 % slower completion time during hypoxia compared to baseline test<br>↑ faster completion time upon returning to normoxia compared to hypoxic testing<br>↔ no difference between BCA and post CA |
| Subudhi (2014) [164]<br><br>*(also see Roach (2014) [163])* | 21 (9 F)/20.8 ± 1.4<br><br>POST7 group: 14<br>POST21 group: 7 | 16-days, field study, from 1,525 m in 3 h with supplemental oxygen up to 5,260 m (passive), after first assessment down to 3800 m for 3-nights, then back up to 5,260 m until day 16;<br>Thereafter descent to 1,525 m for either 7- or 21-days (POST7 or POST21) with return and retesting at 5260 m<br>-<br>Pre-BCA (SL) 30-days pior to expedition at 130 m | Section 1<br>2.1-2.3, 2.5,<br>Section 3<br>5.2 | 4 assessments:<br>Day 1 after arrival (ALT1) and day 16 (ALT16) at 5,260 m;<br>Retesting at 5,260 m after pausing either 7- or 21-days (POST7 or POST21)/NA | DANA[1]:<br>SRT1 & SRT2 (*reaction time*),<br>Procedural Reaction Time (*reaction time*),<br>Go/No-Go (*response inhibition*),<br>Code (Digit symbol) Substitution - simultaneous (*attention*)<br>Code (Digit symbol) Substitution - delayed recall (*short term memory*)<br>Spatial Discrimination (*visuospatial analytic ability*),<br>Match to Sample (*visual memory*),<br>Sternberg's Memory Search (*working memory*) | ↓ 5/9 tests from SL to ALT1 and ↔ normalized back to SL values by ALT16 SRT Tests, Code Substitution - simultaneous, Match to Sample, Procedural Reaction Time<br><br>↔ 4/9 tests from SL to ALT1: Code Substitution - delayed recall, Spatial Discrimination, Go/No-Go, Memory Search<br><br>POST7<br>↔ 2/9 tests retention of acclimatization: Code Substitution – simultaneous, Match to Sample<br>↓ returning to ALT1 values indicating a loss of improvement in tests of reaction time (SRT Tests, Procedural Reaction Time)<br><br>POST21<br>↓ No cognitive function tests showed retention of acclimatization |
| Turner (2015) [200] | 22 (12 F)/23 ± 2 (range 20–28) y | 90 min, Breathing of hypoxic gas mixture via face mask $F_iO_2$ = 10 % ≙ 5,500 m<br>-<br>BCA under normoxia<br>Matched-pairs study with a single-blind, randomised design<br>sham group $F_iO_2$ = 21 % ≙ SL | 1.2-1.3<br>2.1, 2.2, 2.5<br>3.1-3.6<br>4.8, 4.9 | One assessment after 50 min of breathing the gas mixture/40 min | CNS Vital Signs[1]:<br>Verbal and Visual Memory (*verbal memory, visual memory*)<br>Finger Tapping (*psychomotor ability*)<br>Symbol digit coding (*attention*)<br>Stroop Test (*executive function*)<br>Shifting Attention (*executive function*)<br>CPT (*attention*)<br>+<br>Environmental Symptoms Questionnaire | ↓ Hypoxia group: effect of hypoxia was detected for all cognitive domains: neurocognitive index (-20 %), composite memory (-30 %), verbal memory (-34 %), visual memory (-23 %), processing speed (-36 %), executive function (-20 %), psychomotor speed (-24 %), reaction time (-10 %), complex attention (-19 %) and cognitive flexibility (-18 %; all $p < 0.05$);<br>No practice effects |

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|---|---|---|---|---|---|---|
| | | | | | | ↑ Sham group: Practice effects for information processing speed (+30 %), executive function (+14 %), psychomotor speed (+18 %), reaction time (+5 %), cognitive flexibility (+14 %), overall cognitive functioning (+9 %; all $p < 0.05$) |
| Weigle (2007) [187] | 19 (9 F)/M 23.0 ± 3.0 y, F 21.4 ± 0.9 y | 12 days, field study, exposition to altitudes between 4,000 – 14,250 ft ≙ 1,200 – 4,300 m (NA) - BCA at SL | 1.1-1.5 2.1-2.3 Section 3 4.8 | Two assessments at 3,810 m on day 3 and day 6/NA | Visual Motor Reaction Time (*psychomotor ability*) Stroop Color-Word Test (*executive function*) Verbal Reasoning Test: verbally presented problem set needing simple mathematical, spatial, and verbal analytic skills (*mental efficacy, reasoning*) Sentence Repetition (*short term memory*) | Visual Motor Reaction Time ↓ initially 3.2 % slower at 3,810 m, persisted with repeated measurements on day 6 m → impairment only seen in male subjects Stroop Test ↓ initially 27 % longer completion time at 3,810 m ↔ No longer persistent by day 6 ↔ Verbal Reasoning Test and Sentence Repetition at 3,810 m |
| Williams (2019) [201] | 11 (M)/22 ± 4 y | 4 x 60 min in normobaric, environmental chamber, blinded to the condition, $F_iO_2$: 20,93 % ≙ SL; 17,0 % ≙ 1,600 m; 14,5 % ≙ 3,000 m; 12,0 % ≙ 4,500 m - Familiarization session; CA under SL conditions; BCA prior to exposure under supply of normoxic air | 1.1-1.3 2.1-2.3, 2.5, 2.10 Section 3 4.2, 4.7, 4.8 | Assessments respectively after 60 min of exposure/NA | Eriksen flanker (*attention*) N-Back Number Task (*executive function*) Deary–Liewald Reaction Time Task (*reaction time*) | ↓ N-Back Task accuracy at $F_iO_2$ = 14,5 % compared to baseline, 20,93 % and 17,0 %; at $F_iO_2$ = 12,0 % compared to 20,93 % but not to baseline ↔ Eriksen flanker and Deary–Liewald Reaction Time Task performance |
| Zhang (2013) [188] | 46 (M)/20.41 - 1.58 y not part of this review: chronic exposure groups: 3 x 50 subjects each, individuals native to high | 5 days, field study, 3,700 m (NA) - BCA at 300 m | 1.3 2.1-2.5 2.10 | | Neurobehavioral core test battery approved by the WHO Simple Reaction Time Test (*reaction time*), DST-F and DST-B (*short term memory, working memory*), Santa Ana Manual Dexterity Test (*psychomotor ability*), DSST (*attention*), Benton Visual Retention Test (*copying*), | ↓ Santa Ana Manual Dexterity Test, DSST, and Pursuit Aiming Test values decreased after 5 days at 3,700 m compared to their previous SL performance ↔ No change in Simple Reaction Time, DST, and Benton Visual Retention Test |

| First authors | Number of participants (sex)/Mean age of participants (Mean ± SD); profession if mentioned | Study protocol: Time of exposure, experimental condition, altitude profile, maximum altitude reached (Mode of ascent – active/passive) - Study protocol baseline or control group (CG), altitude (test event if named) | STAR core parameters | Timing of neuropsychological test administration under exposure (test event if named)/Duration of Test Battery | Test Battery: Neuropsychological tests (*Cognitive Domain*) + Further investigations that are not part of this review | Changes in cognitive performance ↔ ↑ ↓ based on significant results, $p < 0.05$ (test event if named) |
|---|---|---|---|---|---|---|
| | altitudes of 3,700, 4,500 and 5,100 m | | | | Pursuit Aiming Test (*psychomotor ability*) + Mood state profile | |

Legend:

| | | | |
|---|---|---|---|
| x[1] | Alternate forms used | F | Female |
| A-DST | Auditory Digit Span Test | M | Male |
| ASL | Above sea level | NA | Information not available |
| BART | Balloon Analogue Risk Task | PASAT | Paced Auditory Serial Addition Test |
| BCA | Baseline cognitive assessment | PVSAT | Paced Visual Serial Addition Test |
| CA | Cognitive assessment | PVT | Psychomotor Vigilance Test |
| CG | Control group | RMCPT | Running Memory Continuous Performance Test |
| CPT | Continuous Performance Test | SL | Sea level |
| DANA | Defense Automated Neurobehavioral Assessment Test Battery | SRT | Simple Reaction Time |
| dSRT | Change score = SRT1 minus SRT2 | V-DST | Visual Digit Span Test |
| DSST | Digit Symbol Substitution Test | VWMC | Verbal Working Memory Capacity |
| DST | Digit Span Test | | |
| DST-F | Digit Span Test Forward | | |
| DST-B | Digit Span Test Backward | | |

## 3.3 Consideration and further classification of the reviewed neuropsychological tests

### 3.3.1 Classification according to the cognitive domains studied

In Table 3-3, the neuropsychological tests are grouped according to the cognitive domains studied. In addition, a brief result is given as well as the study conditions. Where the same tests have been used, the studies with field tests are mentioned before the laboratory tests and are ordered by ascending examined altitudes. Additionally, the mode of ascent is given in parentheses. For the sake of completeness, it should be mentioned here that neuropsychological tests were grouped together if the studies showed that they were most likely to be the same test with a slight change in name. For example, the *Digit Symbol Substitution Test* was named the *Symbol Digit Substitution Test* in one study, but has now been combined here. The following is a brief overview and classification of the results. A total of 112 different neuropsychological tests were found, with the *Stroop Test* being the most frequently used with ten applications, eleven if adding the modified version. Overall, of the 173 test applications performed, 74 showed significant impairment, which can be seen in Table 3-4 below.

Cognitive domains with the superordinate term orientation were tested by three studies. Here, the studies conducted in the field by Davranche et al. [8] at 4,350 m and Nelson [182] over 6,500 m yielded impairments.

Twelve different tests were performed to examine attentional capacity in short-term memory. Regarding the field tests, the *Auditory Digit Span Test* showed impairments at 4,280 m in Shi et al. [174] and at 5,100 m in Harris et al. [153], whereas Petiet et al. [184] and Malle et al. [147] found no impairments at higher altitudes in the field. Furthermore, the *Memory Search Task* at 4,330 m for Kramer [158], the *Picture Recognition Test* at 4,280 m for Shi et al. [174], and the *Verbal Free Recall Test* for Pelamatti et al. [183] showed reductions in performance at 4,500 m as well as at 5,040 m. Three laboratory tests examined attention; the *Corsi Block Forwards* and *Digit Span Test-Forward* with De Aquino et al. [194] at 4,500 m and the latter also with Asmaro et al. [6] at 7,620 m showing deteriorations.

In working memory, of 14 performed experiments, seven of them showed changes due to altitude, with four tests in De Aquino's [194] laboratory study at 4,500 m, namely *Corsi Block Backwards*, *Digit Span Test-Backward*, *Random Number Generation*, and *Sequence of Numbers and Letters* showing impairments. Besides that, the *Digit Span Test-Backward* in Asmaro et al. [6] at over 5,334 m and the *Running Memory Continuous Performance* at 4,300 m in Seo

et al. [198] also showed alterations in their first study of 2015. All five tests performed in field showed no alterations.

To investigate focused attention, altitude-induced changes were examined using 20 neuropsychological tests. Limitations in performance were found in the *Code Substitution Task* with Kramer et al. [158] at 4,330 m, with Turner et al. [200] in the *Continuous Performance Test* at 5,500 m, and in four investigations with *Digit Symbol Substitution Test*, starting at 3,269 m [164, 177, 188, 200]. This contrasts with the finding of improvements in the *Digit Symbol Substitution Test* at 5,100 m with Harris et al. [153] and no changes on two other examinations [172] [7]. The *Frankfurt Attention Inventory-2* also showed limitations both in the field and in laboratory testing in Limmer et al. [166]. The *Letter Cancellation Test*, the *Paced Visual Serial Addition Test*, and the *Symbol Digit Modalities Test* showed sensitivity. In the *Paced Auditory Serial Addition Test* all three results from deterioration, improvement, to no change were present. The *Trail Making Test A* showed a decrement in two of five tests, once in the field from 3,500 m with Griva et al. [178] and in the laboratory from 5,334 m with Asmaro et al. [6]. Two tests for response inhibition showed no changes with the *Go/No-Go test*.

Processing speed, mainly objectified by reaction time, was studied in eleven experiments, approx. half of which showed no significant changes in altitude. Limitations were found in different Reaction Time Tests, e.g. in Subudhi et al. [164] in two investigations at 5,260 m. The results by means of the *Psychomotor Vigilance Test* were significantly worse, in Frost et al. [172] at 3,800 m and in Pun & Hartmann [162] at 5,050 m. At an altitude of 2,590 m, Latshang et al. [168] showed no changes in the outcome of the *Psychomotor Vigilance Test*, as did Falla et al. [177] at 3,269 m, although deteriorations correlated with poor sleep. In Harris et al. [153] improved reaction times were found at 5,100 m.

In perception, five of eight trials were unaffected by altitude; *Reading of Briefly Displayed Letters* in Schlaepfer et al. [167] was improved at an altitude of 3,450 m in both the field and the laboratory, whereas the *Pattern Comparison Task* in the study by Kramer et al. [158] showed deterioration at 4,330 m.

For memory, three subcategories were examined in more detail by a total of eight different means. Long-term memory was not affected at altitudes up to 7,100 m [182]. For verbal memory, two positive tests were found, one using *Rey's Auditory-Verbal Learning Test* by Griva et al. [178] at 5,300 m in the field and the *Verbal Memory Test* by Turner et al. [200] at

5,500 m in the laboratory test. Visual memory was impaired on the *Match to Sample Test* by Subudhi et al. [164] at 5,260 m and also by Turner et al.

Two tests for verbal functions showed impairments beyond an altitude of 4,340 m [184, 185].

With regard to construction and motor performance, seven of twelve different tests showed impairments, although these were only examined in one study each. Two tests with multiple occurrences showed different results, such as *Finger Tapping* with a significant deterioration in a laboratory test in Abraini et al. [171] at 5,500 meters. The *Pegboard-Psychomotor Test* showed two deteriorations at an altitude of 5,300 m by Griva et al. [178] and again at 5,500 m by Abraini et al. However, the same examination at 6,265 m by Merz et al. [181] was unremarkable.

For problems requiring concept formatting and reasoning, three of the six studies with six different tests were significantly altered at altitude, two of them with impairment, namely the *Category Search Task* performed at 4,330 m by Kramer et al. [158] and the *Number Ordination - Rey's Test* at 5,500 m by Abraini et al. [171]. However, *Robinson's Numbers Test* results in Phillips et al. [185] however showed improvement at altitude.

With 22 tests and 43 experiments, the executive functions, which include planning and decision-making, were the most extensively studied of the collected studies. Also in this superset, approximately half of the experiments were associated with limitations in executive functions or increased risk behavior. By contrast, three studies objectified improvements or reduced risk behavior at altitude. Regarding the three most common tests *N-Back Number Task*, *Stroop Test,* and *Trail Making Test B*, there are still mixed results. For the *N-Back Number Task*, constraints occurred in the field for the highest altitude tested at 5,160 m by Lefferts et al. [179] and in the only laboratory test at 4,500 m by Williams et al. [201]. The *Stroop Test* was used ten times. In the field examinations the results were very heterogeneous, twice there was no disturbance, twice there was a worsening, but on the follow-up examination there was no further deviation, and finally once there was an improvement. In the laboratory studies, four out of five tests showed worse results in the subjects, the heights investigated ranged from 3,500 m in Chroboczek et al. [190] to 7,620 m in Asmaro et al. [6]. The study by Ochi et al. [192], which investigated three heights from 2,000 to 5,000 m, merely found improvements in reaction time. *Trail Making Test B* revealed impairments in two of five tests, with Griva et al. [178] above 3,500 m in the field and Asmaro et al. [6] above 5,334 m in the laboratory. The field study by Harris et al. [153] elicited improved results at 5,100 m.

Lastly, the remaining domain of affective examinations yielded mixed results in two examinations, with significant deterioration to 4,300 m in Seo et al. [199] and no changes to 4,500 m in Pavlicek et al. [204]. A *Mini-Mental State Examination*, screening multiple cognitive domains, failed to detect any limitations at 4,500 m in the sample examined by Nakano et al. [203].

**Table 3-3 Classification of neuropsychological tests into supercategories of cognitive domains supplemented by article and brief outcome**

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| *Orientation* | | | |
| Spatiotemp-oral integration | Time Wall Estimation Task | Not affected at 3,842 m (LT – HHC)<br>- *Pre-ascent BCA and Post-descent CA at SL* | De Bels (2019) [202] |
| | Time Perception Task | Impaired at 4,350 (FT – P), underestimation of durations<br>- *Familiarization session, CA at SL* | Davranche (2016) [8] |
| Confidence judgement | Feeling of Knowing | Impaired at 6,500 m and 7,100 (FT – A)<br>- *Pre-ascent and approx. 1-week post-descent BCA at 1,200 m* | Nelson (1990) [182] |
| *Attentional capacity, processing speed and working memory* | | | |
| Short term memory | Code (Digit Symbol) Substitution – delayed recall | Not affected at 5,260 m (FT – P)<br>- *Pre-BCA (SL) 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| | Corsi Block Forwards | Impaired 4,500 m (LT – NHC)<br>- *BCA at normoxic conditions, altitude NA* | De Aquino Lemos (2012) [194] |
| | Digit Span Forward | Not affected at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |
| | | Not affected at 3,800 m (FT – NA)<br>- *15-days familiarization with tests 300 ft ≙ 91 m ≙ 752 mm Hg* | Phillips (1963) [185] |
| | | Impaired at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | | Not affected at 5,273 m / 6,348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |

| Cognitive domain | Neuropsychological tests | | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|---|
| | | | Not affected at 7,200 m (FT – A)<br>- *Familiarization trial, 8-days prior to and 4- and 46-days post expedition CA respectively at 1,050 m* | Malle (2016) [147] |
| | | | Impaired at 4,500 m (LT – NHC)<br>- *BCA at normoxic conditions, altitude NA* | De Aquino Lemos (2012) [194] |
| | | | Impaired at 7,620 m (LT – HHC)<br>- *Pre BCA and Post CA, altitude NA* | Asmaro (2013) [6] |
| | | Auditory Digit Span | Impaired at 4,280 m (FT – P)<br>- *BCA "in the plain", altitude NA* | Shi (2016) [174] |
| | | Visual Digit Span | Not affected at 4,280 m (FT – P)<br>- *BCA "in the plain", altitude NA* | Shi (2016) [174] |
| | Memory Search Task | | Impaired at 4,330 m (FT – A)<br>- *Pre-ascent BCA and post-descent CA at 92 m + CG, altitude NA* | Kramer (1993) [158] |
| | Picture Recall Test | | Not affected at 4,280 m (FT – P)<br>- *BCA "in the plain", altitude NA* | Shi (2016) [174] |
| | Picture Recognition Test | | Impaired at 4,280 m (FT – P)<br>- *BCA "in the plain", altitude NA* | Shi (2016) [174] |
| | Pocket Calculator Cognitive Motor Task | | Not affected at 5,400 m (FT – A)<br>- *BCA at 300 m + CG under normoxia* | Bonnon (1999) [175] |
| | Sentence Repetition | | Not affected at 3,109 m / 3,810 m (FT – NA)<br>- *BCA at SL* | Weigle (2007) [187] |
| | Verbal Free Recall | | Impaired at 4,500 m / 5,040 m (FT – A)<br>- *Pre-BCA, twice 15- and 40-days Post-CAs* | Pelamatti (2003) [183] |
| | Word Span Forward | | Not affected at 3,800 m (FT – NA)<br>- *15-days familiarization with tests 300 ft ≙ 91 m ≙ 752 mm Hg* | Phillips (1963) [185] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | | Not affected at 3,800 m (FT – NA)<br>- *Two groups, counterbalanced BCA at SL* | Phillips (1966) [186] |
| Working memory | CogState: Working Memory Task Accuracy | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | Corsi Blocks Backwards | Impaired at 4,500 m (LT – NHC)<br>- *BCA at normoxic conditions, altitude NA* | De Aquino Lemos (2012) [194] |
| | Digit Span Test Backwards | Not affected at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |
| | | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | | Not affected at 7,200 m (FT – A)<br>- *Familiarization trial, 8-days prior to and 4- and 46-days post expedition CA respectively at 1,050 m* | Malle (2016) [147] |
| | | Impaired at 5,334 m / 7,620 m (LT – HHC)<br>- *Pre BCA and Post CA, altitude NA* | Asmaro (2013) [6] |
| | | Impaired at 4,500 m (LT – NHC)<br>- *BCA at normoxic conditions, altitude NA* | De Aquino Lemos (2012) [194] |
| | Memory Interference Task (AB/AC paradigm) | Improved at 4,000 m (LT – BHG)<br>- *Approx. 24 h apart counterbalanced blinded condition with one control CA under normoxia* | Loprinzi (2019) [191] |
| | Operational Span Protocol with VWMC | Not affected at 3,000 m (LT – NHC)<br>- *Practice trial before VWMC, BCA before entering the chamber; Double blind, repeated CA under normobaric normoxia $F_iO_2$ = 20.9 % near SL ≈ 113 m* | Parker (2017) [196] |
| | Random Number Generation | Impaired at 4,500 m (LT – NHC) | De Aquino Lemos |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | | - *BCA at normoxic conditions, altitude NA* | (2012) [194] |
| | Running Memory Continuous Performance Test | Impaired at 4,300 m (LT – NHC)<br>- *Familiarization trial and BCA under normoxia* | Seo (2015) [198] |
| | | Not affected at 4,300 m (LT – NHC)<br>- *Familiarization trial and BCA under normoxia* | Seo (2017) [199] |
| | Sequence of Numbers and Letters | Impaired at 4,500 m (LT – NHC)<br>- *BCA at normoxic conditions, altitude NA* | De Aquino Lemos (2012) [194] |
| | Sternberg's Memory Search | Not affected at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| *Concentration/Focused attention* | | | |
| Attention | Attention Switching Task | Not affected at 5,050 m (FT – P)<br>- *Familiarization trial, 2x BCA and post-expedition CA at 502 m + CG at 1,103 m* | Pun & Guadagni (2018) [161] |
| | Code (Letter Number) Substitution Task | Impaired at 4,330 m (FT – A), insensitive to practice compared to CG<br>- *Pre-ascent BCA and post-descent CA at 92 m + CG, altitude NA* | Kramer (1993) [158] |
| | CogState: Monitoring Task Reaction Time | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | CogState: Monitoring Task Accuracy | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | CogState: Working Memory Task Reaction Time | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | Colorado Perceptual Speed Test | Not affected at 5,300 m (FT – A)<br>- *Pre-ascent BCA and post-descent CA at 1,400 m* | Karinen (2017) [169] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Continuous Performance Test | Not affected at 5,500 m (LT – BHG)<br>- *Pre BCA under normoxia, Post CA* | Altbäcker (2019) [189] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| | Digit Symbol Substitution Test | Impaired at 3,269 m - session 3 (FT – A)<br>- *Familiarization session, BCA at 1,258 m* | Falla (2021) [177] |
| | | Impaired at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |
| | | Not affected at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | | Not affected at 4,554 m (FT – A)<br>- *Pre-study: one night at 2,864 m, Familiarization session, Pre BCA and Post CA at 1,115 m* | Bjursten (2010) [7] |
| | | Improved at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | | Impaired at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| | Divided Attention Steering Simulator | Not affected at 2,590 m (FT – P)<br>- *Pre-ascent BCA and Post-descent CA at 490 m* | Latshang (2013) [168] |
| | Eriksen Flanker | Not affected at 5,160 m (FT – A) | Lefferts (2019) [179] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude | First authors |
|---|---|---|---|
| | | - ***Control condition*** | |
| | | - *Extensive familiarization process prior to the trek, and practice tests throughout the trek; CA prior to expedition at 116 m ASL* | |
| | | Not affected at 4,500 m (LT – NHC) | Williams (2019) [201] |
| | | - *Familiarization session; CA under SL conditions; BCA prior to exposure under supply of normoxic air* | |
| | Frankfurt Attention Inventory-2 | Impaired at 5,339 m (FT – A) | Limmer (2018) [166] |
| | | - *CA prior to expedition at 154 m and post-descent CA at 812 m + CG under normoxia + CG with 7-days physical exercise under normoxia* | |
| | | Impaired at 5,800 m (LT – NHC) | |
| | | - *Pre- and post-CA at 53 m normoxic conditions + CG under normoxia + CG with 7-days physical exercise under normoxia* | |
| | Letter Cancellation Test | Impaired at 3,500 m / 5,300 m (FT – A) | Griva (2017) [178] |
| | | - *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | |
| | Paced Auditory Serial Addition Test | Impaired at 4,280 m (FT – P) | Shi (2016) [174] |
| | | - *BCA "in the plain", altitude NA* | |
| | | Improved at 5273 m / 6348 m (FT – A) | Petiet (1988) [184] |
| | | - *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | |
| | | Not affected at 7,200 m (FT – A) | Malle (2016) [147] |
| | | - *Familiarization trial, 8-days prior to and 4- and 46-days post expedition CA respectively at 1,050 m* | |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Paced Visual Serial Addition Test | Impaired at 4,280 m (FT – P)<br>- *BCA "in the plain", altitude NA* | Shi (2016) [174] |
| | Rapid Visual Processing Test | Not affected at 5,050 m (FT – P)<br>- *Familiarization trial, 2x BCA and post-expedition CA at 502 m + CG at 1,103 m* | Pun & Guadagni (2018) [161] |
| | Ruff 2 & 7 Selective Attention Test | Not affected at 6,265 m (FT – A)<br>- *Familiarization trial, Prior to and 3-months post-expedition CA at 440 m* | Merz (2013) [181] |
| | Selective Auditory Attention Task | Not affected at 5273 m / 6348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |
| | Simple Reaction Time Test Span dSRT | Impaired at 5,260 m (FT – P)<br>- *30-days pior to and 3 months post-expedition CA at SL* | Roach (2014) [163] |
| | Symbol Digit Modalities test | Impaired at 3,500 m / 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | Trail Making Test A | Not affected at 2,590 m (FT – P)<br>- *Pre-ascent BCA and Post-descent CA at 490 m* | Latshang (2013) [168] |
| | | Impaired at 3,500 m / 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | | Not affected at 5050 m (FT – P)<br>- *Familiarization trial, 2x BCA and post-expedition CA at 502 m* | Pun & Hartmann (2018) [162] |
| | | Not affected at 5500 m (FT – A)<br>- *Familiarization trial, Pre-ascent BCA and post-descent CA at 1,400 m, Retesting after return* | Issa (2016) [89] |

| **Cognitive domain** | **Neuropsychological tests** | **Outcome and altitude**<br>**- *Control condition*** | **First authors** |
|---|---|---|---|
| | | | |
| | | Impaired at 5,334 m / 7,620 m (LT – HHC)<br>- *Pre BCA and Post CA, altitude NA* | Asmaro (2013) [6] |
| Response Inhibition | Go/No-Go Test | Not affected at 4,300 m (LT – NHC)<br>- *Familiarization trial and BCA under normoxia* | Seo (2015) [198] |
| | | Not affected at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| *Processing speed* | | | |
| Reaction time | CogState: Simple Reaction Time | Improved at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | Deary-Liewald Reaction Time Task | Not affected at 4,500 m (LT – NHC)<br>- *Familiarization session; CA under SL conditions; BCA prior to exposure under supply of normoxic air* | Williams (2019) [201] |
| | Perceptual Vigilance task | Not affected at 3,842 m (LT – HHC)<br>- *Pre-ascent BCA and Post-descent CA at SL* | De Bels (2019) [202] |
| | Procedural Reaction Time | Impaired at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| | Psychomotor Vigilance Test | Not affected at 2,590 m (FT – P)<br>- *Pre-ascent BCA and Post-descent CA at 490 m* | Latshang (2013) [168] |
| | | Not affected at 3,269 m (FT – A) but higher impairment for poor sleep-ers<br>- *Familiarization session, BCA at 1,258 m* | Falla (2021) [177] |
| | | Impaired at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | | Impaired at 5,050 m (FT – P) | Pun & Hartmann (2018) [162] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | | - *Familiarization trial, 2x BCA and post-expedition CA at 502 m* | |
| | Reaction Time Task | Not affected at 5,050 m (FT – P)<br>- *Familiarization trial, 2x BCA and post-expedition CA at 502 m + CG at 1,103 m* | Pun & Guadagni (2018) [161] |
| | Simple Reaction Time Test | Not affected at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |
| | | Impaired at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| *Perception* | | | |
| Visual perception | Line Bisection Test | Not affected at 6,265 m (FT – A)<br>- *Familiarization trial, Prior to and 3-months post-expedition CA at 440 m* | Merz (2013) [181] |
| | Reading of Briefly Displayed Letters | Improved at 3,450 m (FT – P)<br>- *Familiarization trial, BCA at 540 m* | Schlaepfer (1992) [167] |
| | | Improved at 3,450 m (LT – BHG)<br>- *Familiarization trial, BCA at 540 m* | |
| Visuospatial analytic ability | Abstract Matching | Not affected at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | Line Orientation Task | Not affected at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | | Not affected at 5,273 m / 6,348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |
| | Pattern Comparison Task | Impaired at 4,330 m (FT – A) | Kramer (1993) [158] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude | First authors |
|---|---|---|---|
| | | - ***Control condition*** | |
| | | - *Pre-ascent BCA and post-descent CA at 92 m + CG, altitude NA* | |
| | Spatial Discrimination | Not affected at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| *Memory* | | | |
| Long term memory | FACTRETRIEVAL2 Test Battery | Not affected at 5,400 m / 6,500 m / 7,100 m (FT – A)<br>- *Pre-ascent and approx. 1-week post-descent BCA at 1,200 m* | Nelson (1990) [182] |
| Verbal memory | Rey's Auditory-Verbal Learning Test | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | | Impaired at 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | Selective Reminding Test | Not affected at 5,273 m / 6,348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |
| | Verbal memory test | Not affected at 4,554 m (FT – A)<br>- *Pre-study: one night at 2,864 m, Familiarization session, Pre BCA and Post CA at 1,115 m* | Bjursten (2010) [7] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| Visual memory | CogState: Learning Task Accuracy | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Match to sample | Impaired at 5,260 m (FT – P)<br>- *Pre-BCA 30-days pior to expedition at 130 m* | Subudhi (2014) [164] |
| | Visual Memory Test | Not affected at 4,554 m (FT – A)<br>- *Pre-study: one night at 2,864 m, Familiarization session, Pre BCA and Post CA at 1,115 m* | Bjursten (2010) [7] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| | Visual Object Learning Task | Not affected at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| *Verbal functions and language skills* | | | |
| Speech production and syntax comprehen-sion | Boston Naming Test | Impaired at 5,273 m / 6,348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |
| | Robinson's Rhymes (and Numbers) tests | Impaired at 4,340 m (FT – NA)<br>- *Two groups, counterbalanced BCA at SL* | Phillips (1963) [185] |
| *Construction and motor performance* | | | |
| Copying | Benton Visual Retention Test | Not affected at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |
| Assembling and building | Block Design | Impaired at 3,500 m / 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| Psychomotor ability | Computer-based Psychomotor Speed Task | Impaired at 3,000 m (LT – NHC)<br>- *Familiarization session, CA under normoxia $F_iO_2$ = 20.9 % ≙ 0 m ASL in randomized order* | Pighin (2012) [150] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Finger Tapping | Not affected at 4,330 m (FT – A)<br>- *Pre-ascent BCA and post-descent CA at 92 m + CG, altitude NA* | Kramer (1993) [158] |
| | | Not affected at 4,554 m (FT – A)<br>- *Pre-study: one night at 2,864 m, Familiarization session, Pre BCA and Post CA at 1,115 m* | Bjursten (2010) [7] |
| | | Not affected at 5,273 m / 6,348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| | Motor Praxis Task | Not affected at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | Pegboard-Psychomotor Test | Impaired at 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | | Not affected at 6,265 m (FT – A)<br>- *Familiarization trial, Prior to and 3-months post-expedition CA at 440 m* | Merz (2013) [181] |
| | | Impaired at 5,500 m (LT – HHC)<br>- *3x Pre BCA and 1x Post CA at SL + CG at SL* | Abraini (1998) [171] |
| | Pursuit Aiming Test | Impaired at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Santa Ana Manual Dexterity Test | Impaired at 3,700 m (FT – NA)<br>- *BCA at 300 m* | Zhang (2013) [188] |
| | Surgical Skills | Impaired at 3,000 m (LT – NHC)<br>- *BCA before entering the chamber; Double blind, repeated CA under normobaric normoxia FiO2 = 20.9 % near SL ≈ 113 m* | Parker (2017) [196] |
| | Visual Motor Reaction Time | Impaired at 3,109 m / 3,810 m (FT – NA)<br>- *BCA at SL* | Weigle (2007) [187] |
| Ocular motor performance | King-Devick Test | Impaired at 7,101 m (LT – BHG)<br>- *Familiarization tests, BCA and 3-min post CA at normoxia* | Stepanek (2013) [193] |
| | Saccadic Eye Movement | Not affected at 6,265 m (FT – A)<br>- *Familiarization trial, Prior to and 3-months post-expedition CA at 440 m* | Merz (2013) [181] |
| *Concept formatting and Reasoning* | | | |
| Concept formation | Category Search Task | Impaired at 4,330 m (FT – A)<br>- *Pre-ascent BCA and post-descent CA at 92 m + CG, altitude NA* | Kramer (1993) [158] |
| Mental Efficacy, reasoning | Gorham's Proverbs | Not affected at 5,273 m / 6,348 m (FT – A)<br>- *CA prior to expedition at SL and BCA on Day 6 at 4,000 ft ≙ 1,219 m, Post expedition CA at SL on between 16 to 221 days following the hypoxic exposure* | Petiet (1988) [184] |
| | Number Ordination - Rey's test | Impaired at 5,500 m (LT – HHC)<br>- *3x Pre BCA and 1x Post CA at SL + CG at SL* | Abraini (1998) [171] |
| | Robinson's (Rhymes and) Numbers tests | Improved at 4,340 m (FT – NA)<br>- *Two groups, counterbalanced BCA at SL* | Phillips (1963) [185] |
| | Verbal Reasoning Test | Not affected at 3,109 m / 3,810 m (FT – NA)<br>- *BCA at SL* | Weigle (2007) [187] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| Arithmetic Reasoning Problems | Modified Math Processing Task | Not affected at 3,842 m (LT – HHC)<br>- *Pre-ascent BCA and Post-descent CA at SL* | De Bels (2019) [202] |
| Executive functions | | | |
| Executive function | Attention Shifting Test | Not affected at 4,554 m (FT – A)<br>- *Pre-study: one night at 2,864 m, Familiarization session, Pre BCA and Post CA at 1,115 m* | Bjursten (2010) [7] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| | Category Fluency Tasks | Not affected at 3,000 and 4,500 m (LT – HHC)<br>- *Control profile at 450 m with 200 m "pseudo-ascent" to mask for altitude* | Pavlicek (2005) [204] |
| | Controlled Oral Word Association | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | | Impaired at 3,500 m / 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | Choice Reaction Test (Schuhfried) | Impaired at 3,500 m and 5,500 m (LT – NHC)<br>- *BCA at 450 m ≙ $F_iO_2$ = 20.93 %* | Pramsohler (2017) [197] |
| | CogState: Choice Reaction Time | Not affected at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | Four-Choice Reaction Time | Impaired at 4,000 m / 5,565 m (FT – A)<br>- *4 x CA at 76 – 86 m ASL prior to expedition* | Dykiert (2010) [176] |
| | MATB –Multiple Attribute Task Battery | Impaired at 2,440 m (LT – BHG) | Kourtidou-Papadeli (2008) [170] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude | First authors |
|---|---|---|---|
| | | - ***Control condition*** | |
| | | - *BCA under normoxia with two-week training to establish a personal performance plateau, post exposure CA under 100 % $O_2$* | |
| | N-Back Number Task | Not affected at 2,590 m (FT – P)<br>- *Pre-ascent BCA and Post-descent CA at 490 m* | Latshang (2013) [168] |
| | | Not affected at 3,800 m (FT – P)<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | | Impaired at 5,160 m (FT – A), improved reaction time<br>- *Extensive familiarization process prior to the trek, and practice tests throughout the trek; CA prior to expedition at 116 m ASL* | Lefferts (2019) [179] |
| | | Impaired at 4,500 m (LT – NHC)<br>- *Familiarization session; CA under SL conditions; BCA prior to exposure under supply of normoxic air* | Williams (2019) [201] |
| | Number Comparison Test | Not affected at 5,300 m (FT – A)<br>- *Pre-ascent BCA and post-descent CA at 1,400 m* | Karinen (2017) [169] |
| | One Touch Stockings of Cambridge Task | Not affected at 5,050 m (FT – P)<br>- *Familiarization trial, 2x BCA and post-expedition CA at 502 m + CG at 1,103 m* | Pun & Guadagni (2018) [161] |
| | Pro-Point and Anti-Point Tasks | Not affected at 4,330 m (FT – P)<br>- *Familiarization test, BCA at 344 m prior to expedition* | Gibbons (2020) [173] |
| | Rapid Cognitive Assessment Tool | Not affected at 5,500 m (FT – A)<br>- *Familiarization trial, Pre-ascent BCA and post-descent CA at 1,400 m, Retesting after return* | Issa (2016) [89] |
| | Ruff Figural Fluency Test | Not affected at 6,265 m (FT – A)<br>- *Familiarization trial, Prior to and 3-months post-expedition CA at 440 m* | Merz (2013) [181] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Simon Task | Impaired at 4,350 (FT – P)<br>- *Familiarization session, CA at SL* | Davranche (2016) [8] |
| | Stroop Test | Impaired at 3,109 m, not affected at 3,810 m (FT – NA)<br>- *BCA at SL* | Weigle (2007) [187] |
| | | Impaired at 3,500 m / 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | | Improved at 4,240 m (FT – A)<br>- *CA prior to expedition at 116 m ASL* | Lefferts (2020) [180] |
| | | Not affected at 4,554 m (FT – A)<br>- *Pre-study: one night at 2,864 m, Familiarization session, Pre BCA and Post CA at 1,115 m* | Bjursten (2010) [7] |
| | | Not affected at 5,500 m (FT – A)<br>- *Familiarization trial, Pre-ascent BCA and post-descent CA at 1,400 m, Retesting after return* | Issa (2016) [89] |
| | | Impaired at 3,500 m (LT – BHG)<br>- *Familiarization session, CA under normoxia, altitude NA* | Chroboczek (2021) [190] |
| | | Impaired 4,500 m (LT – NHC)<br>- *BCA at normoxic conditions, altitude NA* | De Aquino Lemos (2012) [194] |
| | | Not affected at 2,000 m / 3,500 m / 5,000 m (LT – BHG), improved reaction time<br>- *Two practice sessions, CA at SL* | Ochi (2018) [192] |
| | | Impaired at 5,500 m (LT – NHC)<br>- *BCA under normoxia, Matched-pairs study with a single-blind, randomised design, sham group $F_iO_2$ = 21 % ≙ SL* | Turner (2015) [200] |
| | | Impaired at 7,620 m (LT – HHC)<br>- *Pre BCA and Post CA, altitude NA* | Asmaro (2013) [6] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| | Number-Size Stroop Variant Task | Not affected at 5,500 m (LT – BHG)<br>- *Pre BCA under normoxia, Post CA* | Altbäcker (2019) [189] |
| | Trail Making Test B | Impaired at 3,500 m & 5,300 m (FT – A)<br>- *BCA at 75 m prior to expedition + CG at/or near SL, altitude NA* | Griva (2017) [178] |
| | | Not affected at 5,050 m (FT – P)<br>- *Familiarization trial, 2x BCA and post-expedition CA at 502 m* | Pun & Hartmann (2018) [162] |
| | | Improved at 5,100 m (FT – A)<br>- *Practice test, CA at SL prior to expedition + CG, altitude NA* | Harris (2009) [153] |
| | | Not affected at 5,500 m (FT – A)<br>- *Familiarization trial, Pre-ascent BCA and post-descent CA at 1,400 m, Retesting after return* | Issa (2016) [89] |
| | | Impaired at 5,334 m / 7,620 m (LT – HHC)<br>- *Pre BCA and Post CA, altitude NA* | Asmaro (2013) [6] |
| | Verbal Letter Fluency | Not affected at 3,000 / 4,500 m (LT – HHC)<br>- *Control profile at 450 m with 200 m "pseudo-ascent" to mask for altitude* | Pavlicek (2005) [204] |
| | Visual Choice Reaction Time | Impaired at 4,330 m (FT – A)<br>- *Pre-ascent BCA and post-descent CA at 92 m + CG, altitude NA* | Kramer (1993) [158] |
| | | Not affected at 6,500 m (LT – HHC)<br>- *3x Pre BCA and 1x Post CA at SL + CG at SL* | Abraini (1998) [171] |

| **Cognitive domain** | **Neuropsychological tests** | **Outcome and altitude**<br>**- *Control condition*** | **First authors** |
|---|---|---|---|
| Planning and decision making | Balloon Analogue Risk Taking task | Risk-taking not affected at 3,269 m - session 4 (FT – A) with faster reaction times and higher earnings<br>- *Familiarization session, BCA at 1,258 m* | Falla (2021) [177] |
| | | Risk-taking not affected at 3,800 m (FT – P) with faster reaction times<br>- *Practice sessions, Group split with pre-ascent BCA or post-descent CA at 340 m ASL* | Frost (2021) [172] |
| | | Impaired, higher risk taking at 3,000 m (LT – NHC)<br>- *Familiarization session, CA under normoxia $F_iO_2$ = 20.9 % ≙ 0 m ASL in randomized order* | Pighin (2019) [149] |
| | Computer-based Risk-Taking Task | Increased risk-taking for choices involving losses at 3,000 m (LT – NHC)<br>- *Familiarization session, CA under normoxia $F_iO_2$ = 20.9 % ≙ 0 m ASL in randomized order* | Pighin (2012) [150] |
| | Game of Dice Task | Increased risk behavior at 4,500 m (LT – NHC) with reduced risk behavior in preacclimatized subjects compared to unacclimatized subjects<br>- *Familiarization session, CG with sham pre-acclimatization 7 × 1 h at FiO2 = 20.9 % ≙ 600 m ASL* | Niedermeier (2017) [195] |
| Further and mixed domains | | | |
| Affective flexibility | Lateralized Tachistoscopic Lexical Decision Task | Not affected at 3,000 / 4,500 m (LT – HHC)<br>- *Control profile at 450 m with 200 m "pseudo-ascent" to mask for altitude* | Pavlicek (2005) [204] |
| | Total Mood Disturbance | Impaired at 4,300 m (LT – NHC)<br>- *Familiarization trial and BCA under normoxia* | Seo (2017) [199] |

| Cognitive domain | Neuropsychological tests | Outcome and altitude<br>- ***Control condition*** | First authors |
|---|---|---|---|
| Unspecified individual test outcome | Mini-Mental State Examination: concentration or working memory, language and praxis, orientation, memory, attention span, and other cognitive factors | Not affected at 4,500 m (LT – HHC)<br>- *No control condition* | Nakano (2015) [203] |

Legend:

FT Field test
- A active mode of ascent
- NA mode of ascent not available
- P passive mode of ascent

LT Laboratory test
- BHG breathing of hypoxic gas mixture
- HHC hypobaric hypoxia chamber
- NHC normobaric hypoxia chamber

ASL Above sea level
BCA Baseline cognitive assessment
CA Cognitive assessment
CG Control group
NA Information not available
SL Sea level

### 3.3.2 Classification according to the numerical frequency of results

Table 3-4 below provides an overview of the frequency of results depending on the research conditions, with test results divided into no alteration, impairment, and improvement. An important note at this point is that this listing only considers the gross test circumstances and results, but not the altitudes associated with the test circumstances. The listing is for descriptive purposes only; other calculations could introduce bias. In the literature, the improvements listed in the tables are most likely attributed to learning effects from the repeated measurements and are not further considered here for simplification reasons.

Of 173 tests applied (sum of field and laboratory tests), 70.5 % were conducted in the field. Of the field tests, slightly more than half of the total 122 test applications were performed under active ascent. Of all tests performed in the field, 60.7 % showed no impairment, 5.7 % showed improvement, and 33.6 % found significant differences in altitude. In active ascent, 60.3 % showed no alteration, and 32.4 % showed deterioration. In passive ascent, 63.2 % of the trials had no alterations, and 34.2 % had deteriorations. Of the 51 laboratory tests, 31.4 % showed no change, in 3.9 % there was an improvement, and 64.7 % showed deterioration in percentage terms. Numerically, in hypoxic gas mixture testings and hypobaric chamber studies, no impairment occurred about as often as impairment. Of the studies with normobaric hypoxia, 82.1 % showed hypoxia-related deterioration.

**Table 3-4 Frequency of neuropsychological test results depending on research condition**

| Research condition | Neuropsychological test application N | | | |
|---|---|---|---|---|
| | Not affected | impairment | improvement | total |
| **FT** | **74** | **41** | **7** | **122** |
| A | 41 | 22 | 5 | 68 |
| NA | 9 | 6 | 1 | 16 |
| P | 24 | 13 | 1 | 38 |
| **LT** | **16** | **33** | **2** | **51** |
| BHG | 3 | 3 | 2 | 8 |
| HHC | 8 | 7 | | 15 |
| NHC | 5 | 23 | | 28 |

FT Field test
- A active mode of ascent
- NA mode of ascent not specified
- P passive mode of ascent

LT Laboratory test
- BHG Breathing of hypoxic gas mixture
- HHC Hypobaric hypoxia chamber
- NHC Normobaric hypoxia chamber

Looking back at Table 3-1, studies conducted in the field were slightly superior in number with 29 expeditions and 31 articles to those 23 conducted in the laboratory. Regarding test applications in Table 3-4, more than twice as many took place in the field than in the laboratory.

## 3.4 Overview of the results

Figure 3-1 and Figure 3-3 provide an overview of the test results in field or in laboratory studies, divided into impairment, no affection, and improvement, plotted against altitude. Regarding the results showing impairment on several levels of altitude, the lowest significant level was chosen. For results without affections at altitude, the highest level of altitude was selected.

In Figure 3-2 and Figure 3-4 the percentages of results with significant impairment in the field vs. in the laboratory studies are plotted against altitude.

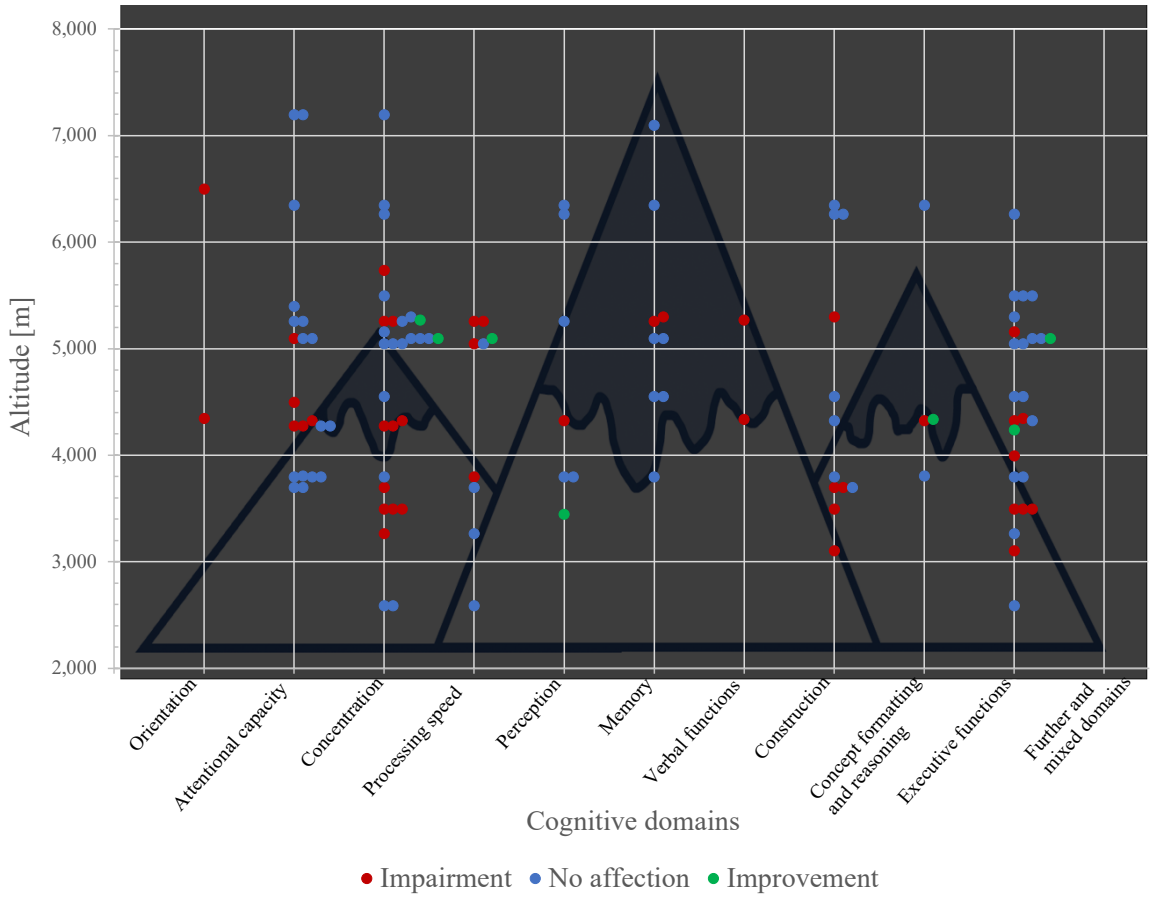


**Figure 3-1 Test results of the field studies with illustration of the different altitudes at which the test applications were conducted**

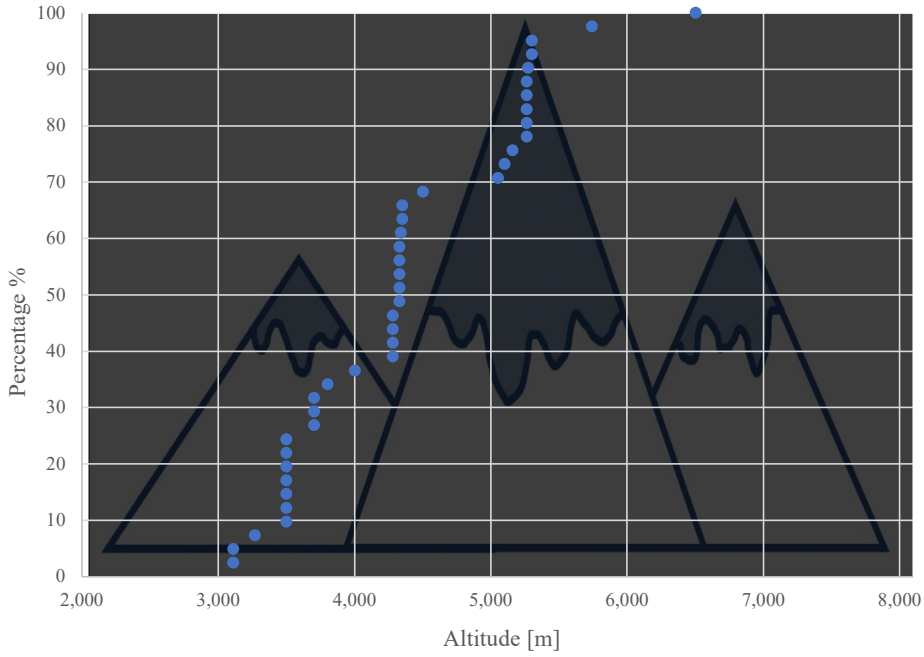


**Figure 3-2 Percentage of field study results with significant impairment against the altitude at which the test applications were conducted**

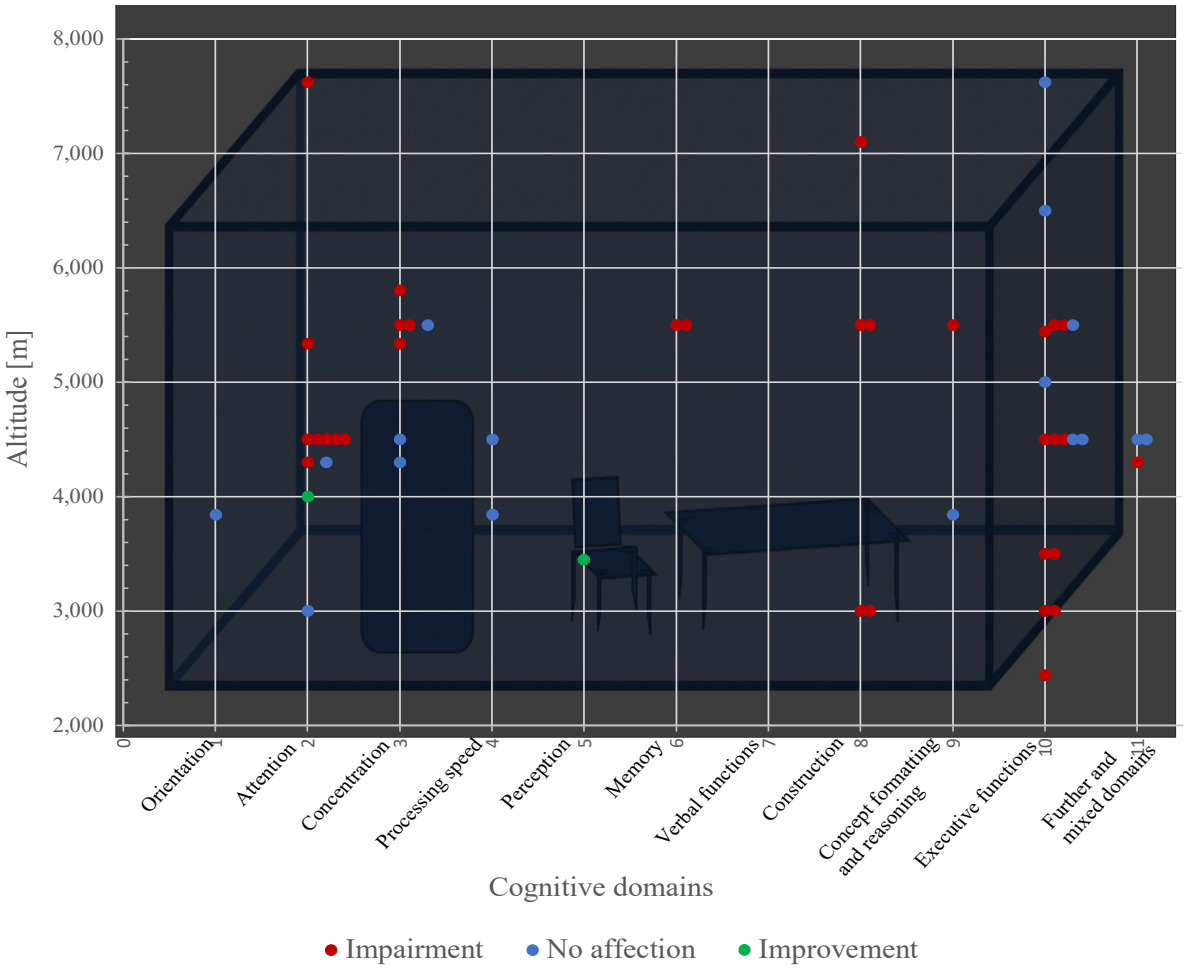


**Figure 3-3 Test results in the laboratory studies**

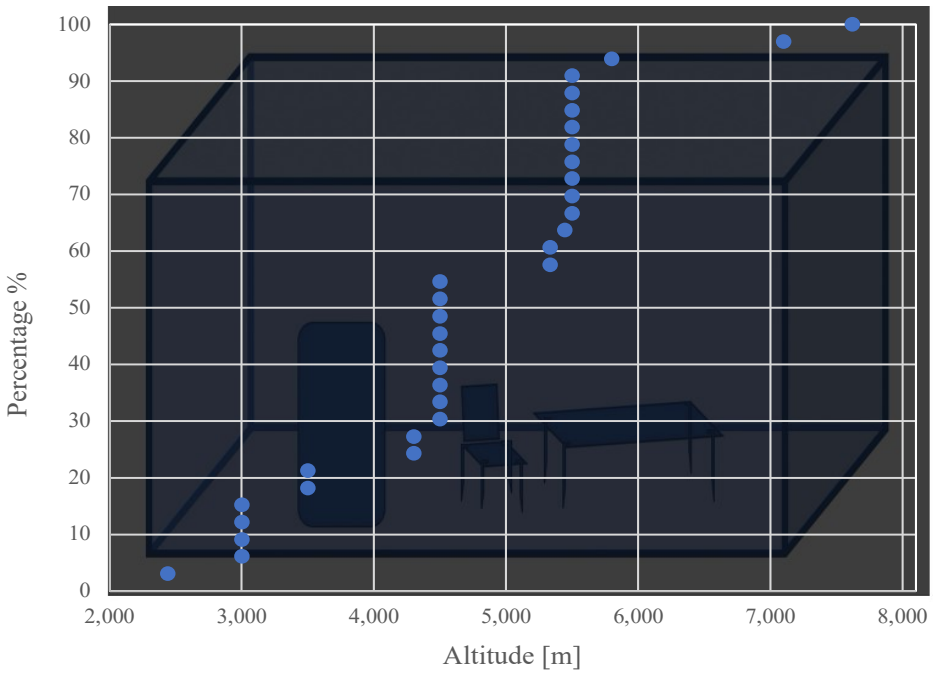


**Figure 3-4 Percentage of laboratory test results with significant impairment against altitude**

# 4. Discussion

## 4.1 Conclusion

The aim of the review was not only to report an overview of the study results and summarize all the evidence for and against cognitive impairment at moderate and high altitudes, but also to subsequently provide a closer look at the neuropsychological tests used. For this purpose, they were listed in such a way so that they were grouped under the respective cognitive domains. The state of research to date indicated in advance that there were heterogeneous results regarding limitations in cognitive performance at moderate to high altitudes.

As was to be expected, some studies indicated impaired cognitive function, while the remaining found no changes or improvements in altitude. In this case, with 74 of 173 test applications, less than half of the experiments found impairment. These discrepancies have so far been explained primarily by differences in the methods used, such as heterogeneous cognitive tasks, performance assessment during a high-altitude expedition or at simulated altitude, with varying duration and severity of hypoxia, and with or without prior acclimatization. Modifications in these parameters are likely to increase within-subject variability and subsequently lead to ambiguous results. This assumption also existed with regard to the results of this review. In summary, the tests used showed a broad picture but impairment could be found. Overall, in all cognitive domains starting with orientation, attentional capacity, attention, perception, memory, verbal functions and language skills, construction and motor performance, concept formatting and reasoning, executive function and finally affective flexibility, study results were found in which cognitive impairment was objectified at altitude.

An innovation over previous reviews was to provide an overview of each neuropsychological test with assignment to its cognitive domain, including explicit mention of its results and certain investigation modalities. For the first time, the tests used were also discussed in more detail. With a total of 173 administrations of neuropsychological tests, the picture is again very heterogeneous, as the number of different tests was 112. Previous studies and reviews often focused on the respective cognitive domains and neglected the actual tests. For better objectification, the particular tests were therefore evaluated in terms of their importance, alongside the outcome as a whole. Although this review is not a meta-analysis, it is still possible to identify trends throughout the presentations and listings. An obvious conclusion would be that there are certain preconditions, such as the altitude level studied, under which results collected with a particular

test can be reproduced. For example, one might expect that tests above a certain altitude would result in significant differences.

A good example that this is partially true can be found in the *Psychomotor Vigilance Test*, which was used in four field studies. In a height-dependent order of the results, two, namely the studies by Frost et al. [172] at 3,800 m and further by Pun & Hartmann [162] at 5,050 m show impairments. The investigation of reaction time using *Psychomotor Vigilance Test* at 2,590 m by Latshang et al. [168] shows no impairments. Interestingly, although the findings of Frost et al. for the investigated altitude of 3,269 m are not significant, a tendency to deterioration could be detected, which was significantly related to a decline in quality of sleep. Therefore, a logical conclusion would be to assume that the abilities of the subjects to respond at sea level are limited with an increase in the altitude of the study. Regarding the *Psychomotor Vigilance Test* in particular, between an altitude of 3,269 m and 3,800 m.

The picture is similar for the *N-Back Number Task*, which was used in four tests and twice showed limitations at altitude. The field test of Frost et al. [172] at 3,800 m is without changes, whereas the laboratory test of Williams et al. [201] at 4,500 m shows significant differences.

That this "threshold altitude" cannot be generalized to other tests appears evident, with reference to the most extensively studied cognitive domain of executive functions. In this domain, a large number of different tests were used, some of which showed no impairment up to very high altitudes, such as the *Ruff Figural Fluency Test* of Merz et al. [181], which showed no deterioration at an altitude of 6,265 m in the field.

As already introduced in the results section, the *Stroop Task* is the most represented with ten applications and the results overview of the studies concerned raise new questions. Namely, of the five field tests, the study conducted at the lowest point at 3,109 m by Weigle et al. [187] deviates from the norm, whereas the study conducted at the highest point at 5,500 m by Issa et al. [89] is found to be unaffected.

To be further discussed from this example, in the field tests, is the consideration of the mode of ascent. Roughly broken down, it can be stated for the passive mode of ascent using cars or mountain cable cars that the rate of ascent is higher than for active ascent on foot. As described before, a slower ascent contributes to better acclimatization [1, 115]. With reference to Davrache et al. [8], better acclimatization would argue for a reduction in the negative effects caused by altitude. The same would have to be true for the laboratory tests, since in most cases the conditions of the altitudes studied were established much faster than they naturally appeared in

comparable field studies. Looking again at the *Stroop Test*, it is noticeable that of the five laboratory tests, impairments were found in four studies, starting at 3,500 m, investigated by Chroboczek et al. [190], up to 7,620 m by Turner et al. [200].

In addition, there seem to be other issues such as test-retest reliability, which can be seen unprecedentedly in the two studies by Seo et al. For example, the first study in 2015 [198] showed significant changes in the *Running Memory Continuous Performance Test*, but the re-run in 2017 [199] could not replicate this result. Assuming that mathematical significance calculations can exclude accidental events, there must be other influencing factors, mediators that have not yet been conclusively clarified. The obvious and already extensively researched ones would be, for example, physical strain, cold, or the quality of sleep.

Regarding the frequency of findings in the examinations, the occurrence of the results was added in Table 3-4 and then calculated as a percentage. In the numerical addition of the test modalities and their results in terms of no alteration, impairment, and improvement, some peculiarities stand out, disregarding of the examined altitudes.

As listed in the results section, there was a slight variation between the number of field and laboratory tests. With regard to the results, however, there were two very clear differences. The first difference concerns the applications of the tests per subject; far more than twice as many test applications took place in the field. In percentage terms as a function of the expedition number, there should have been less than a hundred test applications. We can only theorize about the reasons, but it would be imaginable that in field studies the tests used might be rather unfiltered, according to the motto trial and error, since for example, the resource time is much more available in a base camp during active ascent than in a laboratory experiment. Possibly, the intention of the conducted experiments also plays a role. In the case of passive ascents, the focus is probably mostly on the research idea, which could explain why the number of tests with passive ascents is relatively high in relation to the number of studies. In active ascent field experiments, it is conceivable that neuropsychological testing only plays a subordinate role in mountain expeditions and is virtually a by-product of the actual goal, namely the ascent of a mountain. Laboratory experiments, on the other hand, work in the spirit of research, requiring financial resources specifically directed toward the investigation as additional personnel, equipment, and facility capacity are needed. Therefore, the tests are also used in a focused manner and are more likely to be those that have been shown to be sensitive to altitude-related cognitive changes in previous research.

This brings us to the second difference, which concerns the number of significant results. Proportionally, the tests that found impairments in the field at altitude amounted to about one third of all tests conducted in the field and slightly less than two thirds showed no changes. In contrast, for laboratory tests, the ratio of tests without altitude-induced changes and those with impairments seemed to be almost reversed. This fact represents an innovation over previous review results and is thus a first-time discovery. Regarding the findings from the meta-analysis by McMorris et al. [157] that low $p_aO_2$ is the most important predictor of cognitive performance and that this is independent of whether the exposure is under hypobaric or normobaric hypoxic conditions, this work can arguably add to the findings the component that cognitive performance is proportionally more often impaired in the laboratory studies than in the field studies. The question of where these numbers come from can only be pondered. It is possible that they are related to the aforementioned more rapid onset of compromising circumstances and insufficient acclimatization. As mentioned previously, Martin et al. [24] had concluded that the severity and duration of the altitude exposure had the greatest impact on cognition and that altitude acclimatization appeared to have a positive effect on cognitive performance. Participants in the passive ascents are exposed to hypoxic conditions more rapidly, but the exposure time in hypoxia itself is also usually limited. By contrast, in the field studies, the ascent rate is decisively lower compared to that of the passive field tests. Also, the overall duration is longer than in most laboratory studies, which means that acclimatization can take place over a longer period. In conclusion, this review also suggests that sufficient acclimatization has a beneficial effect on cognitive functions at altitude. Alongside this, however, it must also be mentioned that field excursions with active ascent may have different stressors in the foreground than in the laboratory. Thus, in addition to hypoxia, the stressors in the field may include physical exhaustion from the climb, cold, sleep disturbance, and psychological factors such as stress and anxiety over the climb. In the passive ascents, the problems of inadequate acclimatization are more likely to occur, as measured by the Lake Louise Scale. In the laboratory studies it is probably also the latter. Additionally, in the chamber studies difficulties were caused by the unfamiliar situations, such as the confined space that allows only limited freedom of movement and isolation from the other group members, not to neglect the psychological factors such as claustrophobia. The extent to which these specific factors affect the study results is unclear at this time and needs to be considered.

The assessment of the included data fits very well with the Quality Assessment via the "STAR" data reporting guidelines for clinical high-altitude research. Among others, the application of

the Lake Louise Scale can be found here. The STAR guidelines in the review table assist in monitoring the accuracy of the implementation of the research and the reporting.

## 4.2 Limitations

Throughout this thesis, an attempt has been made to give space to the complexity of the studies analyzed and to list the research modalities and results as completely as possible. On the other hand, the aim was to approach the object of investigation, the effects of hypoxia on cognitive abilities, as straightforwardly and comprehensibly as possible. These intentions are, in view of modern research with consideration of numerous cofactors in the statistical models, contrary to a simple approach. It should be noted that this review addresses the research findings with particular interest and attempts to maintain the claim to completeness and accuracy. At this point, it is therefore important to mention the risk of potential bias in this work. For one thing, this may be the case due to the so-called "publication bias", i.e. the potentially selective reporting of complete studies and non-publication of study results without significant findings. But also "outcome reporting bias" within individual studies has to be discussed as a reason for sources of error.

Despite the broad sample of studies, it must also be mentioned that a large number of studies, some of them highly qualitative, were excluded because they were conducted with military personnel or aircrew. The decision against studies with professional pilots or military personnel is based on the fact that on the one hand highly specialized individuals, e.g. air combat pilots seem to be difficult to compare with mountaineers. Second, the studies were often computer-based multi-tasking assessments (such as used in the study of Kourdidou-Papadeli [170]) that examined occupation-specific scenarios and made it difficult to draw direct conclusions about underlying cognitive functions due to the multifactorial and comprehensive nature of the assignments.

The bundling of the test procedures into supercategories on the basis of the cognitive domain studied was done by drawing artificial dividing lines that are not entirely objectively reproducible. As already noted in the methods section, this artificial simplification is a source of error. One possibility to at least contain it or to standardize it across the studies would also be the creation of a standardized framework of tests. One difficulty and possible bias in classifying the tests was that some of the same neuropsychological tests were used, but their names differed somewhat. In places where this was clearly evident, summaries were made to the same test

name. However, this was probably not successful everywhere, which is one more reason to use standardized test batteries.

## 4.3 Future research directions

From the findings of this review, it can be concluded that the investigation of certain cognitive domains enjoys a high interest in the scientific community. Future studies should therefore try to find a common consensus and complement each other. One possibility would be the creation of a standardized framework of tests, for instance an open access test battery. If used frequently, a standardized test battery could make the different experiments more comparable and help to identify fundamental influencing factors. To date, there have been studies with computerized test batteries, however these were provided by commercial service companies and were therefore only used in occasional studies.

Due to the good objectifiability of the included data with the help of the Quality Assessment via the "STAR" data reporting guidelines for clinical high-altitude research, it can be stated for future studies that the use is quite reasonable. The Guidelines provide investigators with a suggested pathway of quality aspects to examine, reminding for example to collect Setting and Individual factors prior to the study and to record Section 3-5 factors during the execution of the study. In addition, inter-study comparisons can be made quite easily, also because the quality of the study can be made more objective in this way.

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# Appendix

| | Article | Reasons |
|---|---|---|
| 1. | Abeln V, MacDonald-Nethercott E, Piacentini MF, Meeusen R, Kleinert J, Strueder HK, et al. Exercise in isolation-A countermeasure for electrocortical, mental and cognitive impairments. PloS One. 2015; 10(5):e0126356. | Confounding variable: Physical exercise; + 6-week interval between assessments |
| 2. | Algaze I, Phillips L, Inglis P, Lathrop G, Gadbois J, Rizzolo K, et al. Incidence of Mild Cognitive Impairment with Ascending Altitude. High Alt Med Biol. 2020. | No suitable control condition: First tests at 3,500 m |
| 3. | Barkaszi I, Takacs E, Czigler I, Balazs L. Extreme Environment Effects on Cognitive Functions: A Longitudinal Study in High Altitude in Antarctica. Front Hum Neurosci. 2016; 10:331. | Without outcomes of interest: Delayed altitude testing |
| 4. | Bartholomew CJ, Jensen W, Petros TV, Ferraro FR, Fire KM, Biberdorf D, et al. The effect of moderate levels of simulated altitude on sustained cognitive performance. Int J Aviat Psychol. 1999; 9(4):351-9 | Without outcomes of interest: Only one administration of neuropsychological tests; + pilots |
| 5. | Baumgartner RW, Keller S, Regard M, Bartsch P. Flunarizine in prevention of headache, ataxia, and memory deficits during decompression to 4559 m. High Alt Med Biol. 2003; 4(3):333-9. | Drug-related confounding variable: Intake of Flunarizine vs. Placebo |
| 6. | Berry DT, McConnell JW, Phillips BA, Carswell CM, Lamb DG, Prine BC. Isocapnic hypoxemia and neuropsychological functioning. J Clin Exp Neuropsychol. 1989; 11(2):241-51. | Other reasons: No information on duration, exposure time, and corresponding altitude |
| 7. | Bhanushali D, Tyagi R, Limaye Rishi Nityapragya N, Anand A. Effect of mindfulness meditation protocol in subjects with various psychometric characteristics at high altitude. Brain Behav. 2020:e01604. | No control condition: Both assessments conducted at 3,500 m; + Confounding variable mindfulness meditation |
| 8. | Blanchet A, Noel-Jorand MC, Bonaldi V. Discursive strategies of subjects with high altitude hypoxia: extreme environment. Stress medicine. 1997; 13(3):151-8. | Without outcomes of interest: no use of neuropsychological tests |

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| 9. Bolmont B, Bouquet C, Thullier F. Relationships of Personality Traits with Performance in Reaction Time, Psychomotor Ability, and Mental Efficiency during a 31-Day Simulated Climb of Mount Everest in a Hypobaric Chamber. Percept Mot Ski. 2001; 92(3_suppl):1022-30. | Not original research |
| 10. Bolmont Bt, Thullier F, Abraini JH. Relationships between mood states and performances in reaction time, psychomotor ability, and mental efficiency during a 31-day gradual decompression in a hypobaric chamber from sea level to 8848 m equivalent altitude. Physiol Behav. 2000; 71(5):469-76. | Not original research |
| 11. Bouquet CA, Gardette B, Gortan C, Abraini JH. Psychomotor skills learning under chronic hypoxia. NeuroReport. 1999; 10(14):3093-9. | Not original research |
| 12. Bouzat P, Sechaud G, Banco P, Davranche K, Casini L, Baillieul S, et al. The effect of zolpidem on cognitive function and postural control at high altitude. Sleep. 2018; 41(10). | Drug-related confounding variable: Intake of Zolpidem and sleep |
| 13. Cahoon RL. Simple Decision Making at High Altitude. Ergonomics. 1972; 15(2):157-63. | Other reasons: Professional military personnel |
| 14. Carver RP, Winsmann FR. Effect of high elevation upon physical proficiency, cognitive functioning and subjective symptomatology. Percept Mot Skills. 1968; 26(1):223-30. | Drug-related confounding variable: intake of Acetazolamide vs. Placebo |
| 15. Davis JE, Wagner DR, Garvin N, Moilanen D, Thorington J, Schall C. Cognitive and psychomotor responses to high-altitude exposure in sea level and high-altitude residents of Ecuador. J Physiol Anthropol. 2015; 34:2. | No control condition: Only one assessment of lowlanders at high altitude |
| 16. Di Paola M, Bozzali M, Fadda L, Musicco M, Sabatini U, Caltagirone C. Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas. Eur J Neurol. 2008; 15(10):1050-7. | Without outcomes of interest: No cognitive assessment under hypoxia, but 8 weeks before and 8 weeks after ascent |
| 17. Dobashi S, Horiuchi M, Endo J, Kiuchi M, Koyama K. Cognitive Function and Cerebral Oxygenation During Prolonged Exercise Under Hypoxia in Healthy Young Males. High Alt Med Biol. 2016; 17(3):214-21. | Confounding variable: Physical exercise |

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| 18. Evans WO, Witt NF. The interaction of high altitude and psychotropic drug action. Psychopharmacologia. 1966; 10(2):184-8. | Drug-related confounding variable: Intake of psychotropic drugs |
| 19. Feeback MR, Seo Y, Dancy M, Glickman EL. The Effect of Psychomotor Performance, Cerebral and Arterial Blood Saturation between African-American and Caucasian Males Before, During and After Normobaric Hypoxic Exercise. Int J Exerc Sci. 2017; 10(5):655-65. | Confounding variable: Physical exercise<br>+ no data of baseline assessments reported |
| 20. Fowler B, Elcombe DD, Kelso B, Porlier G. The Threshold for Hypoxia Effects on Perceptual- Motor Performance. Hum Factors. 1987; 29(1):61-6. | No control condition |
| 21. Gerard AB, McElroy MK, Taylor MJ, Grant I, Powell FL, Holverda S, et al. Six percent oxygen enrichment of room air at simulated 5,000 m altitude improves neuropsychological function. High Alt Med Biol. 2000; 1(1):51-61. | No control condition |
| 22. Guo W, Chen G, Qin J, Zhang J, Guo X, Yu J, et al. Short-term high-altitude pre-exposure improves neurobehavioral ability. Neuroreport. 2016; 27(6):367-73. | Confounding variable: High-altitude pre-exposure |
| 23. Guo WY, Bian SZ, Zhang JH, Li QN, Yu J, Chen JF, et al. Physiological and psychological factors associated with onset of high-altitude headache in Chinese men upon acute high-altitude exposure at 3700 m. Cephalalgia. 2017; 37(4):336-47. | Confounding variable: High-altitude headache |
| 24. Gustafsson C, Gennser M, Ornhagen H, Derefeldt G. Effects of normobaric hypoxic confinement on visual and motor performance. Aviat Space Environ Med. 1997; 68(11):985-92. | Confounding variable: Shift working |
| 25. Hayashi R, Matsuzawa Y, Kubo K, Kobayashi T. Effects of simulated high altitude on event-related potential (P300) and auditory brain-stem responses. Clin Neurophysiol. 2005; 116(6):1471-6. | ERP measurement |
| 26. Heinrich EC, Djokic MA, Gilbertson D, DeYoung PN, Bosompra NO, Wu L, et al. Cognitive function and mood at high altitude following acclimatization and use of supplemental oxygen and adaptive servoventilation sleep treatments. PloS One. 2019; 14(6):e0217089. | Confounding variable: Sleep treatments |

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| 27. Hoffman CE, Clark RT, Jr., Brown EB, Jr. Blood oxygen saturations and duration of consciousness in anoxia at high altitudes. Am J Physiol. 1946; 145:685-92. | No control condition |
| 28. Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS. The cost to the central nervous system of climbing to extremely high altitude. New Engl J Med. 1989; 321(25):1714-9. | Not original research |
| 29. Hu S, Shi J, Xiong W, Li W, Fang L, Feng H. Oxiracetam or fastigial nucleus stimulation reduces cognitive injury at high altitude. Brain Behav. 2017; 7(10):e00762. | Drug-related confounding variable: Intake of Oxiracetam or fastigial nucleus stimulation (FNS) |
| 30. Jobe JB, Shukitt-Hale B, Banderet LE, Rock PB. Effects of dexamethasone and high terrestrial altitude on cognitive performance and affect. Aviat Space Environ Med. 1991; 62(8):727-32. | Drug-related confounding variable: Intake of Dexamethason vs. Placebo |
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# Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

**Eidesstattliche Versicherung**

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation *Cognition and neuropsychological changes at altitude – a systematic review of literature* selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.
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I hereby confirm that the dissertation *Cognition and neuropsychological changes at altitude – a systematic review of literature* is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.
I further declare that the dissertation submitted here has not been submitted in the same or similar form to any other body for the purpose of achieving an academic degree.

München, den 21.07.2023 Kathrin Bliemsrieder
Munich, July 21, 2023