Effect of acute hypoxia on cognition: a systematic review and meta-regression analysis.

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Abstract

A systematic meta-regression analysis of the effects of acute hypoxia on the performance of central executive and non-executive tasks, and the effects of the moderating variables, arterial partial pressure of oxygen (PaO_2) and hypobaric versus normobaric hypoxia, was undertaken. Studies were included if they were performed on healthy humans; within-subject design was used; data were reported giving the PaO_2 or that allowed the PaO_2 to be estimated (e.g. arterial oxygen saturation and/or altitude); and the duration of being in a hypoxic state prior to cognitive testing was $\leq$ 6 days. Twenty-two experiments met the criteria for inclusion and demonstrated a moderate, negative mean effect size ($g = -.49$, 95% CI -0.64 to -0.34, $p < .001$). There were no significant differences between central executive and non-executive, perception/attention and short-term memory, tasks. Low (35-60 mmHg) PaO_2 was the key predictor of cognitive performance ($R^2 = .45$, $p < .001$) and this was independent of whether the exposure was in hypobaric hypoxic or normobaric hypoxic conditions.

Key words: arterial partial pressure of oxygen; normobaric; hypobaric; central executive; perception; short-term memory; regional cerebral blood flow; catecholamines; glossypharyngeal nerve; carotid body; internal carotid arteries; vertebral arteries

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1. Introduction

The military, mountain rescuers, mountaineers and many other individuals, are required to work and live at high altitudes. With increasing altitude, the barometric pressure decreases exponentially, resulting in a progressive reduction in the ambient partial pressure of oxygen (PO_2), termed hypobaric hypoxia. For practical and logistical reasons, normobaric hypoxia is often used as a laboratory alternative to hypobaric hypoxia, whereby the inspired oxygen fraction is reduced to account for the greater barometric pressure and elicit an 'altitude-equivalent' lowering of PO_2 (Conkin, 2011). An underlying assumption with this isohypoxia approach is that PO_2 is the only relevant physiological stimulus, but there is some evidence for physiological differences elicited by hypobaric hypoxia compared to the isohypoxic, normobaric equivalent (Coppel et al., 2015; Normand & Koehle, 2012;). Nevertheless, both approaches reduce the slope of the oxygen transport cascade from the atmosphere to the mitochondria, eliciting manifold physiological effects resulting primarily from a lower arterial PO_2 (P_aO_2) and reduced oxyhemoglobin saturation (Marconi & Cerretelli, 2008) The precise nature of the response to hypoxic environments is influenced by the magnitude of the stimulus: altitudes up to ~2000-2500 m are in the flat portion of the sigmoidal oxyhemoglobin dissociation curve, whereas higher altitudes are in the steep portion of the curve and require more pronounced adjustment (Lundby et al., 2008). However, broadly speaking, the initial responses to altitude exposure serve to maintain oxygen supply. Hypoxic stimulation of the carotid bodies increases alveolar ventilation, causing respiratory alkalosis (Marconi & Cerretelli, 2008), and augments sympathoadrenal activity, increasing peripheral epinephrine levels (Epi) (Mazzeo & Reeves,

2013), heart rate and cardiac output (Kahler et al., 1962); while peripheral norepinephrine (NE) levels may progressively increase over the initial six-day exposure (Mazzeo & Reeves, 2003).

Within the first hours of exposure, plasma volume also decreases, possibly due to redistribution of fluid from the extra- to intra-cellular fluid compartment (Hannon et al., 1969). Although this reduces total blood volume, red cell volume is unchanged and the oxygen carrying capacity per unit of blood is increased thus augmenting the oxygen delivery for a given cardiac output. Although, in this study, we concentrate on acute hypoxia ($\leq$ 6 days), we should note that with chronic hypoxic exposure (acclimatization) the plasma volume is restored and stimulation of erythopoeisis increases the number of erythrocytes (Pugh, 1964), which, in combination with an increased arterio-venous oxygen difference, enables a reduced cardiac output for a given metabolic oxygen demand (Wolfel et al., 1998). Nevertheless, with both acute and chronic hypoxia, the performance of physical work requiring high rates of aerobic metabolism is impaired, relative to the normoxic work capacity (Pugh, 1967), although this decrement may be lower with normobaric than hypobaric hypoxia (Saugy et al., 2016) and is partially attenuated with acclimation and acclimatization (Pugh 1967).

While the effects of acute hypoxia on physical performance have been studied extensively, there is comparatively little research into the effects on cognitive skills, such as visual search and decision making. These skills typically require attention, perception, executive functioning and short-term memory (STM). Moreover, few authors have attempted to review the work and, to the best of our knowledge, nobody has sought to systematically review this area using meta-analytical methods. Recently, Taylor and colleagues (2016) completed a narrative review and demonstrated a tendency towards inhibition of cognition by acute hypoxia, however these findings were equivocal and inconclusive. In a review focusing primarily on clinical

neuropsychological measures, Virués-Ortega et al. (2004) showed a tendency for acute hypoxia to induce decrements in psychophysiological measures, e.g. P300 latency and amplitude, but this was not always manifest in outcome measures, e.g. reaction time. Although the aforementioned, narrative reviews were unable to provide definitive conclusions, both groups of authors observed similar tendencies, with central executive tasks demonstrating negative effects while the non-executive, perception/attention and short-term memory (STM) tasks showed limited effects. This is in line with studies examining the effects of acute exercise (McMorris & Hale, 2012), heat (Cian et al., 2001; McMorris et al., 2006a) and sleep deprivation (McMorris et al., 2006b) on cognitive function. The findings of Taylor et al. and Virués-Ortega et al. also provide some support for lower PaO_2 resulting in greater inhibition of performance than more moderate levels of PaO_2 (readers not familiar with PaO_2 should note that lower PaO_2 means a greater negative effect of hypoxia than moderate levels of PaO_2). Observation of the studies reviewed by these authors also showed that some studies examined the effect of normobaric hypoxia while others utilized hypobaric hypoxia. Research has suggested that the two conditions may well have different effects on stress due to their differing environmental conditions (Coppel et al., 2015). To summarize the conclusions of Taylor et al. and Virués-Ortega et al., we could say that the empirical literature reviewed provided little strong evidence for a significant effect of hypoxia on cognition but the trend is for an inhibitory effect, especially at low levels of PaO_2 and mainly for central executive tasks.

Given that cognition requires oxygen activation at every stage (Virués-Ortega et al., 2004), one might expect hypoxia to have a resounding negative effect and that the failure of the narrative reviews to demonstrate this unequivocally is counterintuitive. However, animal studies have shown that when PaO_2 falls below ~ 60 mmHg, chemoreceptors in the carotid body sense

the fall and feedback, via the glossypharyngeal nerve, to the the nucleus tractus solitarii (NTS), where they activate tyrosine hydroxylase (TH)-containing catecholaminergic neurons. The NTS projects to the ventrolateral medulla (VLM) (Guyenet et al., 2013) and the paraventricular nucleus of the hypothalamus (King et al., 2013; Rinaman, 2011), regions important in the control of autonomic functions. This results in the release of the catecholamine neurotransmitters NE and Epi. Moreover, catecholaminergic neurons also project to the locus coeruleus (LC) (Abbott et al., 2012; Guyenet et al., 2013), which is the main source of NE in the brain. Release of NE has been shown to increase Ca^{2+} signaling in astrocytes, which is associated with the release of vasodilatory astroglial messengers; dilatation of brain microvessels; and, hence, increases in cerebral blood flow (CBF) (Toussay et al., 2013). Similarly, during hypoxia, feedback to the NTS from visceral afferents and carotid body arterial chemoreceptors has been shown to activate non-TH-containing neurons. These non-catecholaminergic neurons project to the rostral VLM (Guyenet et al., 2013) and, also, stimulate the brain's response to hypoxia. Moreover, adenosine, which is released from the carotid body during hypoxia, plays a role in increasing CBF by stimulating the release of nitric oxide (NO) from vascular endothelium vessels (Ray et al., 2002). NO, mediated by its second messenger cyclic guanosine monophosphate, plays a major role in vasodilation during hypoxia (Umbrello et al., 2012). These hypoxia-induced increases in CBF may account for the apparent disparity between the empirical research results reviewed by Taylor et al. (2016) and Virués-Ortega et al. and what one would expect based on the importance of oxygen during cognition and the lack of it during hypoxia. In other words, increased CBF during hypoxia compensates for lower PaO_2. However, several authors have questioned the ability of increases in hypoxia-induced CBF to ensure a sufficient supply of oxygen for

proficient performance of many tasks, including cognitive functioning (Binks et al., 2008; Ogoh et al., 2013; 2014).

Examination of the results of the studies reviewed by Taylor et al. (2016) and Virués-Ortega et al. (2004) also raises questions concerning the ability of hypoxia-induced increased CBF to ensure maintenance of cognitive performance. Moreover, that many of the studies reviewed had small sample sizes leads one to question their power and it is distinctly possible that, at least, some of these studies displayed Type II errors, which hid a significant deterioration in cognition. We, therefore, decided to carry out a systematic meta-regression analysis, which places the emphasis on effect sizes rather than probability levels, thus compensating for low power. It also allows us to examine the effects of potential modulators on the findings. As a result, firstly, we undertook a test to determine the mean effect size for the effects of acute hypoxia on cognition. Based on the literature, outlined above, concerning increased CBF and the results of the narrative reviews, we hypothesized a significant, main effect of hypoxia on cognition, with a negative mean effect size being demonstrated. Similarly, given that both sets of reviewers argued that results showed a trend for an effect of task type and that research into stress, in general, on animals demonstrates such an effect (see Arnsten, 2009; 2011), our second hypothesis was that central executive tasks would be significantly more negatively affected than non-executive, perception/attention and STM tasks. Our third hypothesis was that low PaO_2 would predict a larger, negative mean effect size than moderate PaO_2. This was based on the fact that the level for moderate hypoxia, which we designated for this study, might not induce feedback by the carotid body to the NTS (Virués-Ortega et al., 2004; West, 2004) and, hence, alter neurotransmitter activity in the brain. Finally, we hypothesized that hypobaric hypoxia would predict poorer cognitive functioning than during normobaric conditions. We also decided

to examine the possibility of an interaction effect between PaO_2 level and normobaric/hypobaric conditions.

2. Method

A systematic literature search, using the following data bases, Pubmed, SCOPUS, SportsDISCUS and Web of Knowledge, was undertaken. Each database was searched from their earliest available record up to September 2016. Key words used in the searches were combinations of “altitude”, “attention”, “central executive”, “cognition”, “hypobaric”, “hypoxia”, “learning”, “long-term memory”, “normobaric”, “perception”, “short-term memory” and “working memory”, In addition, reference lists from empirical reports and reviews were examined and screened for eligibility. Studies were included if they were performed on healthy humans; within-subject design was used; data were reported giving the PaO_2 or that allowed the PaO_2 to be estimated (e.g. arterial oxygen saturation and/or altitude); and the duration of being in a hypoxic state prior to cognitive testing was ≤ 6 days. Studies in which another independent variable was simultaneously administered to the participants (e.g. sleep deprivation) were not included although control conditions, which consisted of hypoxia alone, were included. English language restrictions were applied.

2.1. Selection of studies

Three of the authors selected trials for inclusion. The titles and abstracts of publications obtained by the search strategy were screened. All trials classified as relevant by any of the authors were retrieved. Based on the information within the full reports, we used a standardized form to select the trials eligible for inclusion in the review.

2.2 Data extraction and management

Data were extracted using a customized and predetermined form. This was used to extract relevant data on methodological design, eligibility criteria, interventions (including detailed characteristics of the hypoxic exposure protocols), comparisons and outcome measures. There was no blinding to study author, institution or journal at this stage.

2.3. Data analyses

A mixed effects model, with random effects to combine the studies within each subgroup of dependent variables (central executive tasks, perception/attention tasks and STM tasks) and fixed effects to combine subgroups to yield the main effect, was carried out. Study to study variance was not assumed to be the same and computed within subgroups not pooled across them. The moderators, moderate versus low PaO_2 level and normobaric versus hypobaric hypoxia, and the interaction between the two, were examined using meta-regression analyses (Borenstein et al., 2009). Publication bias was examined using Begg's test (Begg & Mazumdar, 1994).

3. Results

3.1. Included studies.

The characteristics of the included studies can be seen in Table 1. The literature reviewed yielded 68 articles which examined hypoxia and cognition. Of these, 18 met the criteria for inclusion. Four of these articles reported two experiments using different participants in each experiment, therefore these were treated as separate studies, taking the total number of experiments examined to 22. Sixteen experiments included only one task type, while six included two task types. Mean effect sizes were calculated for central executive ($k = 9$), perception/attention ($k = 14$) and STM tasks ($k = 6$) for each study. In total, there were 437 participants. Details of the designs of each experiment can be seen in Table 1.

Insert Table 1 about here

The main effect mean g was -0.49, 95% CI -0.64 to -0.34 ($Z(28) = -4.07$, $p < .001$). Table 1 shows the mean effect sizes for central executive, perception/attention and STM tasks for each experiment. For central executive tasks, all effect sizes were negative. Mean g was -0.44, 95% CI -0.61 to -0.26 ($Z(8) = 5.00$, $p < .001$). There were 10 perception/attention effects sizes that were negative and four positive but the mean g (-0.56, 95% CI -1.22 to 0.10) was non-significant ($Z(13) = 1.67$, $p = .10$). All but one of the STM effect sizes were negative. Mean g was -0.66, 95% CI -0.98 to -0.34 ($Z(5) = 5.19$, $p < .001$). However, a subgroup of dependent variables mixed effects analysis showed that there was no significant effect of task type on these results ($Q(2) = 1.56$, $p = 0.459$). The meta-regression for the PaO_2 variable, with low PaO_2 as the reference category, showed that this was a significant, moderate moderator ($R^2 = .47$, $Q(1) = 14.90$, $p < .001$). The B coefficient ($B = 0.81$) demonstrates smaller, negative effect sizes as PaO_2 increases from low to moderate levels. For the normobaric versus hypobaric variable, with normobaric hypoxia as the reference category, there was a borderline effect ($R^2 = .29$, $Q(1) = 3.99$, $p = .046$). The B coefficient ($B = 0.50$) represents decreases in negativity of effect sizes from normobaric to hypobaric conditions. However, the interaction model showed that PaO_2 was by far the better predictor of effect size ($B = 0.75$, $p < .002$), with the normobaric versus hypobaric variable adding nothing significant to the model ($B = 0.14$, $p = .581$). The interaction model showed slightly less variation in effect sizes ($R^2 = .45$, $Q(1) = 14.72$, $p < .001$) than that for PaO_2 alone. Examination of the funnel plot, using Begg's test, demonstrated no significant publication bias (Kendall's $\tau = .076$, $p = .28$), although we should note that power of this test is only moderate when N= 22 (Begg & Mazumdar, 1994).

4. Discussion

This is the first review to systematically examine the effect of acute hypoxia on central executive, perception/attention and STM tasks, and the effect of the moderating variables, low versus moderate PaO_2 and normobaric versus hypobaric conditions, and the interaction between the two variables. The results of this meta-analysis supply only limited support for our hypotheses. Firstly, as hypothesized, the main effect showed a moderate, negative mean effect size and is evidence for a significant, inhibitory effect of acute hypoxia on cognition. This supports the conclusions of the narrative reviewers (Taylor et al., 2016; Virués-Ortega et al., 2004), but the strength of the effect is greater than one might have expected from the probability-based results on which both sets of reviewers relied. Counterintuitively, however, we failed to support our hypothesis that central executive tasks would show higher, negative effect sizes compared to the non-executive tasks, i.e. perception/attention and STM tasks. Our hypothesis that low PaO_2 would predict a larger, negative mean effect size than moderate hypoxia was supported. Finally, the findings examining the use of normobaric versus hypobaric conditions are less transparent. Normobaric conditions predict poorer performance, with a moderate R^2 (.29), while the interaction with PaO_2 accounted for much more of the variation (R^2 = .45). This is only 2% lower than the variation accounted for by PaO_2 alone, therefore showing that it is PaO_2 that significantly accounts for the results.

That the main mean effect size was only moderate is not surprising when one takes into account the fact that this included studies where cognition was tested at both moderate (61 mmHg to 89 mmHg) and low (< 60 mmHg) levels of PaO_2. The cut-off level for low PaO_2, in this study, was set at a measure which is about the level at which physiological studies have shown the initiation of a response by the carotid body to the lowering of PaO_2 (Feldman et al., .2013; West, 2004). In other words, in humans and other animals, it is not until this threshold is

reached that the organism perceives the necessity for action to attempt to maintain homeostasis. Therefore, one would not expect any substantial negative effects on cognition until this level had been reached. This is supported by the meta-regression data for low and moderate PaO_2 levels. The B coefficient (0.81) and moderate to high R^2 (.47) show that PaO_2 level is a strong predictor of deterioration in cognitive performance, with performance weaker at low levels of PaO_2. This suggests that when PaO_2 level is low (< 60 mmHg), increased CBF is unable to compensate for the lack of oxygen sufficiently enough for cognitive performance levels to be maintained. However, several researchers (Lewis et al., 2014; Ogoh et al., 2013; Subudhi et al., 2014) have demonstrated that alterations in regional CBF (rCBF) are more important than those in global CBF (gCBF), with respect to cognition. For example, examination of the effect of hypoxia on rCBF in internal carotid arteries (ICA) shows a different effect to that in vertebral arteries (VA). These authors reported that there was increased rCBF in both ICA and VA, during acute hypoxia, but that in VA was the larger. VA serve the cerebellum, hypothalamus, thalamus, basal ganglia and brainstem, regions of the brain concerned with cardiorespiratory control (Binks et al., 2008; Lewis et al., 2014). However, ICA supply cerebral cortex regions involved in cognition (Binks et al., 2008). Thus it would appear that in the case of hypoxia, the organism places the emphasis on control of the cardiorespiratory system, which is vital for survival, rather than on areas of the brain involved in cognition. However, it is important to note that at the levels of hypoxia covered in this analysis, the individual is still capable of cognition albeit of a lower quality. At very low levels of PaO_2, this is not maintained (see Wagner, 2010).

Despite the fact that Taylor et al. (2016) and Virués-Ortega et al. (2004) showed trends towards central executive tasks being more negatively affected by hypoxia than perception/attention and STM tasks, and that animal research with a multitude of stressors has

also demonstrated this (Arnsten, 2009; 2011), we failed to show any significant differences in mean effect sizes between task types. Before examining these results in more detail, we will outline the differences between the tasks. Central executive tasks are part of what Baddeley (1986) termed working memory. According to Baddeley, working memory consists of three separate but inter-dependent parts, the central executive mechanism, and two STM systems, the phonological loop and the visuospatial sketch pad. The phonological loop is responsible for the encoding of acoustic and verbal information. The visuospatial sketchpad has the same role as the phonological loop except that it processes visual and visuospatial information. The role of the central executive is to integrate the perceptual input and compare the present situation (held in STM) with recalled information from long-term memory. Miyake et al. (2000) described the central executive process as involving several functions, which include shifting between tasks or mental sets; updating and monitoring working memory representations, which involves the removal of redundant information and replacing it with new, relevant information; inhibition of prepotent responses; planning; and the coordination of multiple tasks. Leh et al. (2010) provided other examples, e.g. abstract thinking, cognitive flexibility and selecting relevant sensory information. Positron Emission Tomography and functional Magnetic Resonance Imaging research has shown that central executive tasks primarily activate the prefrontal cortex (PFC) but also draw on information recalled from other parts of the brain (see Barbas, 2000; Leh et al., 2010, for reviews).

Perception/attention tasks are as those tasks which require focusing on and/or identifying relevant stimuli then carrying out a comparatively simple, pre-determined response (McMorris, 2016). These are tasks such as simple and choice reaction time, visual search and coincidence anticipation. In general, the first stage of such tasks requires activation of the specific sensory

region or regions involved. Information extracted from the sensory cortices is passed to the sensory association areas and the PFC where it is integrated and interpreted. The level of integration and interpretation varies between tasks but these tasks are generally thought of as being more simple than working memory tasks. In this study, when we refer to STM tasks, we are describing tasks which require simply acquiring the information and immediately recalling it. They are processed similarly to perceptual ability tasks. When STM is part of working memory and plays an important role in central executive task performance, the PFC and the the dorsal frontoparietal attention network are activated (Braunlich et al., 2015). In this study, such tasks have been determined as being central executive tasks.

Our reasons for expecting differences in effects of hypoxia on the different task types was not based solely on empirical data and narrative reviews but also had a theoretical base. During stress, these tasks are greatly affected by the activity of the neurotransmitters dopamine (DA), NE and 5-hydroxytryptamine (5-HT: also known as serotonin), the peptide corticotropin releasing factor (CRF), and the hormones adrenocorticotrophin hormone (ACTH) and cortisol. Moreover, animal studies have shown that during hypoxia, feedback from chemoreceptors in the carotid body stimulate catecholaminergic and serotonergic neurons in the NTS (Chen et al., 2000; Wang & Fitzgerald, 2002), while CRF, ACTH and cortisol are synthesized and released from the hypothalamic-pituitary-adrenal (HPA) axis, modulated by the action of NE and its receptors in the paraventricular nucleus of the hypothalamus (Chen et al., 2004). Research with animals and humans has shown that during high levels of stress of any kind, NE in the LC is synthesized and released to other parts of the brain. Moreover, LC neurons also project to the ventral tegmental area (VTA), where they activate α_1-adrenoceptors, which induce enhanced glutamate release thus potentiating the firing of DA neurons (Mejías-Aponte et al., 2009). High

concentrations of NE activate the low affinity α_1- and β-adrenoceptors (Arnsten, 2011) in the PFC. Furthermore, within the PFC, glucocorticoids further stimulate activation of α_1-adrenoceptors and D_1-receptors (Shansky & Lipps, 2013). The activation of α_1-adrenoceptors reduces neuronal firing, while increased stimulation of D_1-receptors and β-adrenoceptors induces even greater activity of the second messenger, cyclic adenosine monophosphate, which dampens all neuronal activity, thus weakening the signal to 'noise' ratio (Arnsten, 2011). Hence, we expected to see cognitive performance of central executive tasks inhibited, as they require activation of the PFC.

Stress research with animals has shown that the situation with regard to non-executive tasks, which rely on activation of the sensory cortices and their association areas, is different. High concentrations of NE activating α_1- and β-adrenoceptors can positively affect signal detection (Waterhouse et al., 1980; 1981). Moreover, research has also shown that this can be increased by CRF and 5-HT stimulation of the LC-NE system. CRF causes tonic firing of LC-NE neurons, which results in suppression of somatosensory signal transmission within the somatosensory thalamus and cortex (Devilbiss et al., 2012). This appears to reduce detectability of low-intensity stimuli without affecting high-intensity stimuli (Devilbiss & Waterhouse 2002; Moore, 2004). Arnsten (2009) saw this as a defense mechanism by which the organism increases its ability to detect high priority, dangerous stimuli and allows it to ignore non-threatening stimuli. Therefore, we thought that it was possible that such tasks, particularly perception/attention tasks, might be facilitated by low oxygen levels or, at least, unaffected. However, our results failed to support this, with no significant differences between tasks.

The rationale that hypoxia would result in facilitation of non-executive tasks was based on the fact that animal research has shown that hypoxia induces the release of DA, NE,

glucocorticoids and 5-HT in the brain (Chen et al., 2000; Erickson & Millhorn, 1984), which should result in facilitation of non-executive tasks in the manner explained in the previous paragraph. However, all task types were inhibited, with no significant differences between them. Our findings are probably best explained by the work of Gibson and colleagues (Gibson et al., 1981; Gibson & Peterson, 1982). They claimed that although animal and human studies have shown that during hypoxia, brain concentrations of DA and NE are not reduced, turnover most likely is. The fall in turnover appears to be due to the requirement for oxygen during the synthesis, release and metabolism of the catecholamine and serotonin neurotransmitters (Davis & Carlsson, 1973; Gibson et al., 1981; Gibson & Peterson, 1982; Shukitt-Hale et al., 1993). As a result, during low levels of oxygen, poor performance of all cognitive tasks is due to a lack of activity by DA, NE and 5-HT. This would have the same effect as low catecholamines and 5-HT concentrations in the brain which, in line with inverted-U theory (Yerkes & Dodson, 1908), is thought to inhibit performance of all types of task (Cooper, 1973; Decamp & Schneider, 2009; Kumar et al., 2011). When neurotransmitter concentrations are low, the appropriate sequence of neuronal activation cannot be obtained as a result of neurons being at such a low level of excitation that they cannot be stimulated to an adequate level of summation.

The current findings regarding the use of normobaric versus hypobaric hypoxic conditions are inconclusive. There was a trend toward a significant regression ($p = .046$), and low R^2 (.29) and B (0.50), which suggests that normobaric hypoxia may be associated with greater reductions in cognitive function. However, when the interaction between PaO_2 level and normobaric versus hypobaric conditions was examined, the latter had no significant moderating effect on the outcome. This is despite the fact that levels of NO have been shown to increase vasodilation during hypoxia (Umbrello et al., 2012) and these are lower in hypobaric conditions,

resulting in greater oxidative stress than in the normobaric condition (Faiss et al., 2013; Hemmingsson & Linnarsson, 2009). However, our data would strongly suggest that when determining the effect of hypoxia on cognition, PaO_2 level is the key factor, regardless of whether it is in hypobaric or normobaric conditions.

4.1. Limitations

The conclusions of the current review are only applicable when PaO_2 levels range from 89 mmHg to 35 mmHg and for a duration of 10 mins to 5 days. When PaO_2 is at very low levels, e.g. those found near the summit of Mount Everest ($PaO_2 < 30$ mmHg; West, 2004), cognition becomes severely inhibited (Wagner, 2010). Currently, there is significant debate regarding the effects of acclimatization on cognition (Malle et al., 2016; Rimoldi et al., 2016) and we considered this topic outside the scope of the current review. We should note however that the effects of acclimatization may be associated to the action of the transcription factor, hypoxia-inducible factor (HIF), which binds with hypoxia response element (HRE), to upregulate production of erythropoietin, angiogenic factors and glucose transporters (Bruick, 2003), which may help consolidate cognition.

With regard to the cognitive tasks used in the studies included in the current review, we feel it is imperative to highlight that there were no long-term memory tasks. Hypoxia has been shown to induce the release of brain derived neurotrophic factor, important for long-term potentiation and memory formation, therefore one might expect a positive effect. However, this appears to be dependent on activation of DA receptors (Wang et al., 2006) and, as we have seen, the activity of DA is inhibited by acute hypoxia. Similarly, hypoxia also induces release of acetylcholine (Ach) in the NTS via the carotid body-glossypharyngeal nerve pathway (Guyenet et al., 2013). Ach has been shown to play a major role in developing long-term memory (Blake et

al., 2014; Parent & Baxter, 2004). However, Gibson and Peterson (1981) showed that Ach synthesis, release and metabolism was inhibited by low levels of oxygen. Despite this, research into the effects of hypoxia on long-term memory is still very much required.

Unfortunately, this review and meta-analysis is limited by the number of and quality of the included studies, and also suffers from the limited number of studies. The small number of studies limited the number of potential modulators that we could examine. For example, the range of time of measuring cognition post-initial exposure to hypoxia ranged from 10 mins to 5 days. This may have had an effect on performance. Moreover, none of the included studies incorporated the assessment of neurochemical measurements to support their findings.

5. Conclusion

In conclusion, the key findings to emerge from this this review are a) hypoxia has a negative effect on cognition, b) this is regardless of whether the task is central executive or a non-executive perception/attention or STM task, and c) it is likely that PaO_2 level, and not whether the exposure is in hypobaric hypoxic or normobaric hypoxic conditions, is the key predictor of cognitive performance.

6. References

* Included in meta-analyses

1 Abbott, S.B,, Kanbar, R., Bochorishvili, G., Coates, M.B., Stornetta, R.L., Guyenet, P.G., 2012. C1 neurons excite locus coeruleus and A5 noradrenergic neurons along with sympathetic outflow in rats. J. Physiol. 590, 2897–915.

2 *Ando, S., Hatamoto, Y., Sudo, M., Kiyonaga, A., Tanaka, H., Higaki,, Y., 2013. The effects of exercise under hypoxia on cognitive function. PLoS ONE 8(5): e63630. doi:10.1371/journal.pone.0063630

3 Arnsten, A.F.T., 2009. Stress signalling pathways that impair prefrontal cortex structure and function, Nat. Rev. Neurosci. 10, 410–422.

4 Arnsten, A.F.T., 2011. Catecholamine influences on dorsolateral prefrontal cortical networks, Biol. Psychiatry. 69, e89–e99, http://dx.doi.org/10.1016/j.biopsych. 2011.01.027

5 *Asmaro, D., Mayall, J., Ferguson, S., 2013. Cognition at altitude: impairment in executive and memory processes under hypoxic conditions. Aviat. Space Environ. Med. 11, 59-65.

6 Baddeley, A.D. 1986. Working Memory, Oxford University Press, New York.

7 Barbas, H., 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices, Brain Res. Bull. 52, 319–330.

8 Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics. 50, 1088-1101.

9 Binks, A.P., Cunningham, V.J., Adams, L. Banzett, R.B, 2008. Gray matter blood flow change is unevenly distributed during moderate isocapnic hypoxia in humans. J. Appl. Physiol. 104, 212–217,

10 Blake, M.G., Krawczyk, M.C., Baratti, C.M., Boccia, M.M., 2014. Neuropharmacology of memory consolidation and reconsolidation: Insights on central cholinergic mechanisms. J. Physiol. 108, 286–291.

11 *Bonnon, M., Noël-Jorand, MC., Therme, P., 1999. Criteria for psychological adaptation to high-altitude hypoxia. Percept. Mot. Skills. 89, 3-18.

12 Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Introduction to Meta-Analysis. John Wiley and Sons, Chichester.

13 Braunlich, K., Gomez-Lavin, J., Seger, C.A., 2015. Frontoparietal networks involved in categorization and item working memory, NeuroImage. 107, 146–162

14 Bruick, R.K., 2003. Oxygen sensing in the hypoxic response pathway: regulation of the hypoxia-inducible transcription factor. Genes Dev. 17, 2614–2623.

15 Chen, J., He, L., Dinger, B., Fidone, S., 2000. Stimulus-specific signaling pathways in rabbit carotid body chemoreceptors. Neurosci. 95, 283–291.

16 Chen, X-Q., Du, J-Z., Wang, Y.S., 2004. Regulation of hypoxia-induced release of corticotropin-releasing factor in the rat hypothalamus by norepinephrine. Regul. Peptides. 119, 221– 228.

17 Cian, C., Barraud, P.A., Melin, B., Raphel C., 2001. Effects of fluid ingestion on cognitive function after heat stress or exercise-induced dehydration. Int. J. Psychophysiol. 42, 243-251.

18 Conkin, J. 2011. PH_2O and simulated hypobaric hypoxia. Aviat. Space Environ. Med. 82, 1157-1158.

19 Cooper, C.J., 1973. Anatomical and physiological mechanisms of arousal with specific reference to the effects of exercise. Ergonomics. 16, 601-609.

20 Coppel, J., Hennis, P., Kawai, E. G., Grocott, M.P.W., 2015. The physiological effects of hypobaric hypoxia versus normobaric hypoxia: a systematic review of crossover trials. Ext. Physiol. Med. 4:2. doi 10.1186/s13728-014-0021-6.

21 Davis, J.N., Carlsson, A., 1973. The effect of hypoxia on monoamine synthesis, levels and metabolism in rat brain J. Neurochem. 21, 783-790.

22 Decamp, E., Schneider, J.S., 2009. Interaction between nicotinic and dopaminergic therapies on cognition in a chronic Parkinson model. Brain Res. 1262, 109-114.

23 Devilbiss, D.M., Waterhouse, B.D., 2002. Determination and quantification of pharmacological, physiological, or behavioral manipulations on ensembles of simultaneously recorded neurons in functionally related neural circuits, J. Neurosci. Methods. 121, 181–198.

24 Devilbiss, D.M., Waterhouse, B.D., Berridge, C.W., Valentino, R., 2012. Corticotropin-releasing factor acting at the locus coeruleus disrupts thalamic and cortical sensory-evoked responses, Neuropsychopharmacol. 37, 2020–2030.

25 Erickson, J.T, Millhorn, D.E., 1994. Hypoxia and electrical stimulation of the carotid sinus nerve induce Fos-like immunoreactivity within catecholaminergic and serotoninergic neurons of the rat brainstem. J. Comp. Neurol. 348, 161-182.

26 Faiss, R., Pialoux, V., Sartori, C., Faes, C., Dériaz, O., Millet, G.P., 2013. Ventilation, oxidative stress, and nitric oxide in hypobaric versus normobaric hypoxia. Med. Sci. Sports Exerc. 45, 253-60.

27 Feldman, J.L., McCrimmon, D.R., Morrison, S.F., 2013. Neural control of respiratory and cardiovascular functions, In: Squire, L.R., Berg, D., Bloom, F.E., du Lac, S., Ghosh, A., Spitzer, N.C. (Eds), Fundamental Neuroscience, 4th edition, Elsevier Academic Press, New York, pp. 749-766.

28 *Fowler, B., Prlic, H., Brabant, M., 1994. Acute hypoxia fails to influence two aspects of short-term memory: implications for the source of cognitive deficits. Aviat. Space Environ. Med. 65, 641-645.

29 Gibson, G.E., Peterson, C., 1982. Decreases in the release of acetylcholine *in vitro* with low oxygen. Biochem. Pharmacol. 31, 111-115,

30 Gibson, G.E., Pulsinelli, W., Blass, J.P., Duffy, T.E., 1981. Brain dysfunction in mild to moderate hypoxia. Am. J. Med. 70, 1247-1254.

31 Guyenet, P.G., Stornetta, R.L., Bochorishvili, G., DePuy, S.D., Burke, P.G.R., Abbott, S.B.G., 2013. C1 neurons: the body's EMTs. Am. J. Physiol. Regul. Integr. Comp. Physiol. 305, R187–R204.

32 Hannon, J.P., Shields, J.L., Harris, C.W. 1969. Effects of altitude acclimatization on blood composition of women. J. Appl. Physiol. 26, 540-547.

33 *Hayashi, R., Matsuzawab, Y., Kubob, K.. Toshio Kobayashi, T., 2005. Effects of simulated high altitude on event-related potential (P300) and auditory brain-stem responses. Clin. Neurophysiol. 116, 1471–1476.

34 Hemmingsson, T., Linnarsson, D., 2009. Lower exhaled nitric oxide in hypobaric than in normobaric acute hypoxia. Respir. Physiol. Neurobiol. 169, 74-77.

35 Kahler, R.L., Goldblatt, A., Braunwald, E. 1962. The effects of acute hypoxia on the systemic venous and arterial systems and on myocardial contractile force. J. Clin. Invest. 41, 1553-1563.

36 King, T.L., Kline, D.D., Ruyle, B.C., Heesch, C.M., Hasser, E.M., 2013. Acute systemic hypoxia activates hypothalamic paraventricular nucleus-projecting catecholaminergic

490 neurons in the caudal ventrolateral medulla. Am. J. Physiol. Regul. Integr. Comp.
491 Physiol. 305,:R1112-R1123.
492 37 *Komiyama, T., Sudo, M., Higaki, Y., Kiyonaga, A., Tanaka, H., Ando, S., 2015. Does
493 moderate hypoxia alter working memory and executive function during prolonged
494 exercise? Physiol. Behav. 139, 290–296.
495 38 Kumar, A.M., Ownby, R.L., Waldrop-Valverde, D., Fernandez, B., Kumar, M.J., 2011.
496 Human immunodeficiency virus infection in the CNS and decreased dopamine
497 availability: relationship with neuropsychological performance. Neurovirol. 17, 26-40.
498 39 Leh, S.E., Petrides, M., Strafella, A.P., 2010. The neural circuitry of executive functions
499 in healthy subjects and Parkinson's disease, Neuropharmacol. 35, 70–85.
500 40 Lewis, N.C.S., Messinger, L., Monteleone, B., Ainslie, P.N., 2014. Effect of acute
501 hypoxia on regional cerebral blood flow: effect of sympathetic nerve activity. J. Appl.
502 Physiol. 116, 1189–1196.
503 41 *Li, P., Zhang, G., You, H-Y., Zheng, R., Gao, Y-Q., 2012. Training-dependent cognitive
504 advantage is suppressed at high altitude. Physiol. Behav. 106, 439–445.
505 42 Lundby, C., Marconi, C., Cerretelli, P., Levine, B.D. 2008. Human adaptation to altitude
506 and hypoxia: ethnic differences, chronic adaption and altitude training. In: Taylor,
507 N.A.S., Groeller, H. (Eds.), Physiological Bases of Human Performance during Work and
508 Exercise. Elsevier, Philadelphia, pp-447-457.
509 43 Malle, C., Ginon, B., Bourrilhon, C., 2016. Brief working memory and physiological
510 monitoring during a high-altitude expedition. High Alt. Med. Biol.
511 doi:10.1089/ham.2016.0022 [Epub ahead of print].

512 44 Marconi, C., Cerretelli. P. 2008. Altitude physiology: the impact of hypoxia on human
513 performance. In: Taylor, N.A.S., Groeller, H. (Eds.), Physiological Bases of Human
514 Performance during Work and Exercise. Elsevier, Philadelphia, pp-433-446.
515 45 Mazzeo, R., Reeves, J.T. 2003. Adrenergic contribution during acclimatization to high
516 altitude: perspectives from Pikes Peak. Exerc. Sport Sci. Rev. 31, 13-18.
517 46 McMorris, T., 2016. Developing the catecholamines hypothesis for the acute exercise-
518 cognition interaction in humans: lessons from animal studies. Physiol. Behav. 165, 291-
519 299.
520 47 McMorris, T., Hale, B.J., 2012. Differential effects of differing intensities of acute
521 exercise on speed and accuracy of cognition: a meta-analytical investigation. Brain Cogn.
522 80, 338-351.
523 48 McMorris, T., Swain, J., Smith, M., Harris, R.C., Corbett, J., Delves, S., Sale, C., Potter,
524 J., 2006a. Heat stress, plasma concentrations of epinephrine, norepinephrine, 5-
525 hydroxytryptamine and cortisol, perception of mood state and working memory. Int. J.
526 Psychophysiol. 61, 204-215.
527 49 McMorris, T., Harris, R.C., Swain, J., Corbett, J., Collard, K., Dyson, R, Dye, L.,
528 Hodgson, C., Draper, N., 2006b. Effect of creatine supplementation and sleep
529 deprivation, with mild exercise, on cognitive and psychomotor performance, mood state,
530 and plasma concentrations of catecholamines and cortisol. Psychopharmacol. 185, 93-
531 103.
532 50 Mejías-Aponte, C.A., Drouin, C., Aston-Jones, G., 2009. Adrenergic and noradrenergic
533 innervation of the midbrain ventral tegmental area and retrorubral field: prominent inputs
534 from medullary homeostatic centers, J. Neurosci. 29, 3613–3626.

51 Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis, Cogn. Psychol. 41, 49–100

52 Moore, C.I., 2004. Frequency-dependent processing in the vibrissa sensory system, J. Neurophysiol. 91, 2390–2399.

53 *Noble, J., Jones, J.G., Davis, E.J., 1993. Cognitive function during moderate hypoxaemia. Anaesth. Intensive Care. 21, 180-184.

54 Normand, R.A., Koehle, M.S. 2012. Differences in cardio-ventilatory responses to hypobaric and normobaric hypoxia: a review. Aviat. Space Environ. Med. 83, 677-684.

55 Ogoh, S., Nakahara, H., Ueda, S., Okazaki, K., Shibasaki, M., Subudhi, A.W., Miyamoto, T., 2014. Effects of acute hypoxia on cerebrovascular responses to carbon dioxide. Exp. Physiol. 99, 849–858.

56 Ogoh, S., Sato, K., Nakahara, H., Okazaki, K., Subudhi, A.W., Miyamoto, T., 2013. Effect of acute hypoxia on blood flow in vertebral and internal carotid arteries. Exp. Physiol. 98, 692–698.

57 Parent, M.B., Baxter, M.G., 2004. Septohippocampal acetylcholine: involved in but not necessary for learning and memory? Learn. Mem. 11, 9-20.

58 *Pavlicek, V., Schirlo, C., Nebel, A., Regard, M., Koller, E.A., Brugger, P., 2005. Cognitive and emotional processing at high altitude. Aviat. Space Environ. Med. 76, 28-33.

59 Pugh, L.G.C.E. 1964. Blood volume and haemoglobin concentration at altitudes above 18,000 ft.(5500 m). J. Physiol. 170, 344-354.

60 Pugh, L.G.C.E. 1967. Athletes at altitude. J. Physiol., 192, 619-646.

61 Ray, C.J., Abbas, M.R., Coney, A.M., Marshall, J.M., 2002. Interactions of adenosine, prostaglandins and nitric oxide in hypoxia-induced vasodilatation: *in vivo* and *in vitro* studies. J. Physiol. 544, 195–209.

62 Rimoldi, S.F., Rexhaj, E., Duplain, H., Urben, S., Billieux, J., Allemann, Y., Romero, C., Ayaviri, A., Salinas, C., Villena, M., Scherrer, U., Sartori, C., 2016. Acute and chronic altitude-induced cognitive dysfunction in children and adolescents. J. Pediatr. 169, 238-243.

63 Rinaman, L. 2011. Hindbrain noradrenergic A2 neurons: diverse roles in autonomic, endocrine, cognitive, and behavioral functions, Am. J. Physiol. Regul. Integr. Comp. Physiol. 300, R222–R235.

64 Saugy, J.J., Rupp, T., Faiss, R., Lamon, A., Bourdillon, N., Millet, G. P. 2016. Cycling time trial is more altered in hypobaric than normobaric hypoxia. Med. Sci. Sports Exerc. 48, 680-688.

65 *Schlaepfer, T.E., Bärtsch, P., Fisch, H.U., 1992. Paradoxical effects of mild hypoxia and moderate altitude on human visual perception. Clin. Sci. 83, 633-636.

66 Shansky, R.M., Lipps, J., 2013. Stress-induced cognitive dysfunction: hormone-neurotransmitter interactions in the prefrontal cortex Front. Hum. Neurosci. 7. doi: 103389/fnhum201300123.

67 *Shukitt-Hale, B., Banderet, L.E., Lieberman, H.R., 1998. Elevation-dependent symptom, mood, and performance changes produced by exposure to hypobaric hypoxia. Int. J. Aviat. Psychol. 8, 319-334.

579 68 Shukitt-Hale, B., Stillman, M.J., Levy, A., Devine, J.A., Lieberman, H.R., 1993.
580 Nimodipine prevents the in vivo decrease in hippocampal extracellular acetylcholine
581 produced by hypobaric hypoxia. Brain Res. 621, 291-295.
582 69 *Singh, S.B., Thakur, L., Anand, J.P., Yadav, D., Amitabh, Banerjee, P.K., 2004. Effect
583 of chronic hypobaric hypoxia on components of the human event related potential. Indian
584 J. Med. Res. 120, 94-99.
585 70 *Stepanek, J., Cocco, D., Pradhan, G.N., Smith, B.E., Bartlett, J., Studer, M., Kuhn, F.,
586 Cevette, M.J., 2013. Early detection of hypoxia-induced cognitive impairment using the
587 King-Devick test. Aviat. Space Environ. Med. 84, 1017-1022.
588 71 *Stepanek, J., Pradhan, G.N,, Cocco, D., Smith, B.E., Bartlett, J., Studer, M., Kuhn, F.,
589 Cevette, M.J., 2014. Acute hypoxic hypoxia and isocapnic hypoxia effects on
590 oculometric features. Aviat. Space Environ. Med. 85, 700-707.
591 72 Subudhi, A.W., Fan, J-L., Evero, O., Bourdillon, N., Kayser, B., Julian, C.J., Lovering,
592 A.T., Roach, R.C., 2014. AltitudeOmics: effect of ascent and acclimatization to 5260 m
593 on regional cerebral oxygen delivery. Exp. Physiol. 99, 772–781.
594 73 Taylor, L., Watkins, S., Marshall, H., Dascombe, B., Foster, J., 2016. The impact of
595 different environmental conditions on cognitive function: a focused review. Front.
596 Physiol. doi: 10.3389/fphys.2015.00372.
597 74 Toussay, X., Basu, K., Lacoste, B., Hamel, E., 2013. Locus Coeruleus stimulation
598 recruits a broad cortical neuronal network and increases cortical perfusion. J. Neurosci.
599 33, 3390 –3401.

75 *Tsarouchas, N., Benedek, K., Bezerianos, A., Benedek, G., Keri, S., 2008. Effects of moderate hypobaric hypoxia on evoked categorical visuocognitive responses. Clin. Neurophysiol. 119, 1475-1485.

76 Umbrello, M., Dyson, A., Feelisch, M., Singer, M., 2012. The key role of Nitric Oxide in hypoxia: hypoxic vasodilation and energy supply–demand matching. Antiox. Redox Signal. doi: 10.1089/ars.2012.4979.

77 Virués-Ortega, J., Buela-Casal, G., Garrido, E., Alcázar, B., 2004. Neuropsychological functioning associated with high-altitude exposure. Neuropsychol. Rev. 14, doi: 10.1007/s11065-004-8159-4.

78 Wagner, P.D., 2010. Operation Everest II. High Alt. Med. Biol. 11, 111-119.

79 Wang, H-Y., Fitzgerald, R.S., 2002. Muscarinic modulation of hypoxia-induced release of catecholamines from the cat carotid body Brain Res. 927, 122–137.

80 Wang, H., Yuan, G., Prabhakar, N.R.,Boswell, M., Katz, D.M., 2006. Secretion of brain-derived neurotrophic factor from PC12 cells in response to oxidative stress requires autocrine dopamine signaling. J. Neurochem. 96, 694–705.

81 Waterhouse, B.D, Moises, H.C., Woodward, D.J., 1980. Noradrenergic modulation of somatosensory cortical neuronal responses to iontophoretically applied putative transmitters. Exp. Neurol. 69, 30-49.

82 Waterhouse, B.D., Moises, H.C., Woodward, D. J., 1981. Alpha-receptor-mediated facilitation of somatosensory cortical neuronal responses to excitatory synaptic inputs and iontophoretically applied acetylcholine. Neuropharmacol. 20, 907-920.

83 *Wesensten, N.J., Crowley, J., Balkin, T., Kamimori, G., Iwanyk, E., Pearson, N., Devine, J., Belenky, G., Cymerman, A., 1993. Effects of simulated high altitude exposure

on long-latency event-related brain potentials and performance. Aviat. Space Environ. Med. 64, 30-36.

84 West, J.B., 2004. The physiologic basis of high-altitude diseases. Ann. Intern. Med. 141:789-800.

85 *Wu, X., Li, X., Han, L., Wang, T., Wei, Y., 1998. Effects of acute moderate hypoxia on human performance of arithmetic. Space Med. Med. Eng. (Beijing). 11, 391-395.

86 Wolfel, E.E., Selland, M.A., Cymerman, A., Brooks, G.A., Butterfield, G.E., Mazzeo, R.S., Grover, R.F., Reeves, J.T. 1998. O_2 extraction maintains O_2 uptake during submaximal exercise with β-adrenergic blockade at 4,300 m. J. Appl. Physiol. 85, 1092-1102.

87 Yerkes, R.M., Dodson, J.D. 1908. The relation of strength of stimulus to the rapidity of habit formation. J. Comp. Neurol. Psychol. 18, 459-482.

88 *Zhang, G., Zhou, S.M., Yuan, C., Tian, H.J., Li, P., Gao, Y.Q., 2013. The effects of short-term and long-term exposure to a high altitude hypoxic environment on neurobehavioral function. High Alt. Med. Biol. 14, 338-341.

639 Table 1. Effect sizes for central executive, perception/attention and short-term memory tasks,
640 and characteristics of the studies included in the meta-analysis.

Authors	N	Estimated PaO_2[a]	Normobaric or hypobaric	Cognitive task	Hedges' g (SE[e])	95% CI[i] interval Lower	Upper
Shlaepfer et al. (1992) Experiment 1	10	67 mmHg	hypobaric	Attention task[c]	0.96 (0.45)	0.07	1.85
Shlaepfer et al. (1992) Experiment 2	10	62 mmHg	normobaric	Attention task[c]	1.92 (0.53)	0.89	2.94
Noble et al. (1993)	12	50 mmHg	normobaric	choice reaction time[c]	-1.17 (0.43)	-2.01	-0.33
Wesensten et al. (1993)	10	60 mmHg	normobaric	auditory oddball[b]	-0.16 (0.11)	-0.37	0.05
Fowler et al. (1994) Experiment 1	12	35 mmHg	normobaric	dichotic listening[c]	-2.11 (0.50)	-2.01	-0.33
Fowler et al. (1994)	12	35 mmHg	normobaric	short-term memory[d]	-3.09 (0.60)	-4.26	-1.92

Experiment 2							
Shukitt-Hale et al. (1998)	23	57 mmHg: 61 mmHg	normobaric	Tower of London[b] choice reaction time[c] simple reaction time[c] attention tasks[c]	-0.10 (0.05)[f] -0.43 (0.25)[g]	-0.19 -0.91	-0.002 0.06
Wu et al. (1998)	16	66 mmHg: 60 mmHg: 54 mmHg	normobaric	simple mathematics[c]	-0.89 (0.11)	-1.11	-0.69
Bonnon et al. (1999)	7	67 mmHg: 51 mmHg	hypobaric	attention task[c]	-0.44 (0.23)	-0.90	0.01
Singh et al. (2004)	20	70 mmHg: 61 mmHg	hypobaric	auditory oddball[b]	-0.23 (0.15)	-0.53	0.08

Pavlicek et al. (2005) Group 1	7	87 mmHg: 59 mmHg	normobaric	word generation[c]	0.55 (0.87)	-1.15	2.25
Pavlicek et al. (2005) Group 2	7	87 mmHg: 72 mmHg	normobaric	word generation[c]	0.81 (0.89)	-0.94	2.55
Hayashi et al. (2005)	17	60 mmHg	normobaric	auditory oddball[b]	-0.50 (0.07)	-0.63	-0.37
Tsarouchas et al. (2008)	10	58 mmHg	normobaric	go/no go[b]	-0.41 (0.14)	-0.69	-0.14
Li et al. (2012) Group 1	54	63 mmHg	hypobaric	visual choice reaction time[c] auditory choice reaction time[c] pursuit aiming[c] forward digit recall[d] backward digit recall[d] Benton visual retention test[d]	-0.65 (0.02)[g] -0.24 (0.01)[h]	-0.68	-0.62 -0.23
Li et al. (2012)	51	63 mmHg	hypobaric	visual choice reaction time[c]		-0.32	-0.26

Group 2				auditory choice reaction time[c]	-0.29 (0.02)[g]		
				pursuit aiming[c]			
				forward digit recall[d]			
				backward digit recall[d]	-0.26 (0.01)[h]	-0.28	-024
				Benton visual retention test[d]			
Ando et al. (2013)	12	89 mmHg: 75 mmHg	normobaric	go/no go[a]	-0.52 (0.06)	-0.63	-0.40
Asmaro et al. (2013)	35	52 mmHg: 37 mmHg	normobaric	Stroop color test[b]	-0.57 (0.03)[f]	-0.64	-0.51
				trail making B[b]			
				trail making A[c]	-3.61 (0.02)[g]	-3.65	-3.57
				forward digit recall[d]	-1.66 (0.03)[h]	-1.71	-1.61
				backward digit recall[d]			

Stepanek et al. (2013)	25	40 mmHg	normobaric	King-Devick test[c]	-1.13 (0.02)	-1.17	-1.07
Zhang et al. (2013)	46	65 mmHg	hypobaric	choice reaction time[c]	-0.34 (0.01)[g]	-0.37	-0.32
				pursuit aiming[c]			
				forward digit recall[d]	-0.25 (0.01)[h]	-0.27	-0.23
				backward digit recall[d]			
				Benton visual retention[d]			
Stepanek et al. (2014)	25	35 mmHg: 40 mmHg	normobaric	King-Devick test[c]	-0.71 (0.04)	-0.76	-0.64
Komiyama et al. (2015)	16	75 mmHg	normobaric	go/no go[b]	-0.64 (0.35)[f]	-1.34	0.05
				spatial delay response[d]	0.10 (0.35)[h]	-0.57	0.78

Note. [a] PaO_2 (arterial partial pressure of oxygen) was estimated from actual altitude, estimated altitude equivalent or mean oxygen saturation, hence values are only approximate.

[b] central executive task

[c] perception/attention task

[d] short-term memory task

[e] SE standard error

[f] g for central executive tasks

[g] g for perception/attention tasks

[h] g for short-term memory tasks

[i] CI confidence interval