# 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 $\leq 6$ 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 $\alpha_1$-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 $\alpha_1$- and β-adrenoceptors (Arnsten, 2011) in the PFC. Furthermore, within the PFC, glucocorticoids further stimulate activation of $\alpha_1$-adrenoceptors and $D_1$-receptors (Shansky & Lipps, 2013). The activation of $\alpha_1$-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 $\alpha_1$- 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.

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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]<br>choice reaction time[c]<br>simple reaction time[c]<br>attention tasks[c] | -0.10 (0.05)[f]<br>-0.43 (0.25)[g] | -0.19<br>-0.91 | -0.002<br>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]<br>auditory choice reaction time[c]<br>pursuit aiming[c]<br>forward digit recall[d]<br>backward digit recall[d]<br>Benton visual retention test[d] | -0.65 (0.02)[g]<br><br><br><br>-0.24 (0.01)[h] | -0.68<br><br><br><br>-0.26 | -0.62<br><br><br><br>-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 |

641

642 Note. [a] $PaO_2$ (arterial partial pressure of oxygen) was estimated from actual altitude, estimated

643 altitude equivalent or mean oxygen saturation, hence values are only approximate.

644 [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