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

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3 Terry McMorris<sup>a,b,c\*</sup>, Beverley J. Hale<sup>b</sup>, Martin Barwood<sup>d</sup>, Joseph Costello<sup>a</sup>, Jo Corbett<sup>a</sup>

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5 <sup>a</sup>Department of Sport and Exercise Science, Faculty of Science, University of Portsmouth,

6 Guildhall Walk, Portsmouth PO1 2ER, United Kingdom

7 <sup>b</sup>Department Sport and Exercise Science, Institute for Sport, University of Chichester, College

8 Lane, Chichester, West Sussex PO19 6PE, United Kingdom

9 <sup>c</sup>Department of Psychology, Faculty of Health and Life Sciences, Northumbria University,

10 Northumberland Road, Newcastle-upon-Tyne NE1 8ST, United Kingdom

11 <sup>d</sup>Department of Sport, Health and Nutrition, Leeds Trinity University, Brownberrie Lane,

12 Horsforth LS18 5HD, United Kingdom

13 \*Address for correspondence: 63 Four Winds Court, Hartlepool TS26 0LP, United Kingdom

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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<sub>2</sub>) 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<sub>2</sub> or that allowed the PaO<sub>2</sub> 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<sub>2</sub> 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; glossopharyngeal nerve; carotid body; internal carotid arteries; vertebral arteries

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

39 1. Introduction

40 The military, mountain rescuers, mountaineers and many other individuals, are required  
41 to work and live at high altitudes. With increasing altitude, the barometric pressure decreases  
42 exponentially, resulting in a progressive reduction in the ambient partial pressure of oxygen  
43 ( $PO_2$ ), termed hypobaric hypoxia. For practical and logistical reasons, normobaric hypoxia is  
44 often used as a laboratory alternative to hypobaric hypoxia, whereby the inspired oxygen fraction  
45 is reduced to account for the greater barometric pressure and elicit an ‘altitude-equivalent’  
46 lowering of  $PO_2$  (Conkin, 2011). An underlying assumption with this isohypoxia approach is that  
47  $PO_2$  is the only relevant physiological stimulus, but there is some evidence for physiological  
48 differences elicited by hypobaric hypoxia compared to the isohypoxic, normobaric equivalent  
49 (Coppel et al., 2015; Normand & Koehle, 2012;). Nevertheless, both approaches reduce the slope  
50 of the oxygen transport cascade from the atmosphere to the mitochondria, eliciting manifold  
51 physiological effects resulting primarily from a lower arterial  $PO_2$  ( $P_aO_2$ ) and reduced  
52 oxyhemoglobin saturation (Marconi & Cerretelli, 2008) The precise nature of the response to  
53 hypoxic environments is influenced by the magnitude of the stimulus: altitudes up to ~2000-  
54 2500 m are in the flat portion of the sigmoidal oxyhemoglobin dissociation curve, whereas  
55 higher altitudes are in the steep portion of the curve and require more pronounced adjustment  
56 (Lundby et al., 2008). However, broadly speaking, the initial responses to altitude exposure serve  
57 to maintain oxygen supply. Hypoxic stimulation of the carotid bodies increases alveolar  
58 ventilation, causing respiratory alkalosis (Marconi & Cerretelli, 2008), and augments  
59 sympathoadrenal activity, increasing peripheral epinephrine levels (Epi) (Mazzeo & Reeves,

60 2013), heart rate and cardiac output (Kahler et al., 1962); while peripheral norepinephrine (NE)  
61 levels may progressively increase over the initial six-day exposure (Mazzeo & Reeves, 2003).

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

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

83 neuropsychological measures, Virués-Ortega et al. (2004) showed a tendency for acute hypoxia  
84 to induce decrements in psychophysiological measures, e.g. P300 latency and amplitude, but this  
85 was not always manifest in outcome measures, e.g. reaction time. Although the aforementioned,  
86 narrative reviews were unable to provide definitive conclusions, both groups of authors observed  
87 similar tendencies, with central executive tasks demonstrating negative effects while the non-  
88 executive, perception/attention and short-term memory (STM) tasks showed limited effects. This  
89 is in line with studies examining the effects of acute exercise (McMorris & Hale, 2012), heat  
90 (Cian et al., 2001; McMorris et al., 2006a) and sleep deprivation (McMorris et al., 2006b) on  
91 cognitive function. The findings of Taylor et al. and Virués-Ortega et al. also provide some  
92 support for lower PaO<sub>2</sub> resulting in greater inhibition of performance than more moderate levels  
93 of PaO<sub>2</sub> (readers not familiar with PaO<sub>2</sub> should note that lower PaO<sub>2</sub> means a greater negative  
94 effect of hypoxia than moderate levels of PaO<sub>2</sub>). Observation of the studies reviewed by these  
95 authors also showed that some studies examined the effect of normobaric hypoxia while others  
96 utilized hypobaric hypoxia. Research has suggested that the two conditions may well have  
97 different effects on stress due to their differing environmental conditions (Coppel et al., 2015).  
98 To summarize the conclusions of Taylor et al. and Virués-Ortega et al., we could say that the  
99 empirical literature reviewed provided little strong evidence for a significant effect of hypoxia on  
100 cognition but the trend is for an inhibitory effect, especially at low levels of PaO<sub>2</sub> and mainly for  
101 central executive tasks.

102         Given that cognition requires oxygen activation at every stage (Virués-Ortega et al.,  
103 2004), one might expect hypoxia to have a resounding negative effect and that the failure of the  
104 narrative reviews to demonstrate this unequivocally is counterintuitive. However, animal studies  
105 have shown that when PaO<sub>2</sub> falls below ~ 60 mmHg, chemoreceptors in the carotid body sense

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

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

130 Examination of the results of the studies reviewed by Taylor et al. (2016) and Virués-  
131 Ortega et al. (2004) also raises questions concerning the ability of hypoxia-induced increased  
132 CBF to ensure maintenance of cognitive performance. Moreover, that many of the studies  
133 reviewed had small sample sizes leads one to question their power and it is distinctly possible  
134 that, at least, some of these studies displayed Type II errors, which hid a significant deterioration  
135 in cognition. We, therefore, decided to carry out a systematic meta-regression analysis, which  
136 places the emphasis on effect sizes rather than probability levels, thus compensating for low  
137 power. It also allows us to examine the effects of potential modulators on the findings. As a  
138 result, firstly, we undertook a test to determine the mean effect size for the effects of acute  
139 hypoxia on cognition. Based on the literature, outlined above, concerning increased CBF and the  
140 results of the narrative reviews, we hypothesized a significant, main effect of hypoxia on  
141 cognition, with a negative mean effect size being demonstrated. Similarly, given that both sets of  
142 reviewers argued that results showed a trend for an effect of task type and that research into  
143 stress, in general, on animals demonstrates such an effect (see Arnsten, 2009; 2011), our second  
144 hypothesis was that central executive tasks would be significantly more negatively affected than  
145 non-executive, perception/attention and STM tasks. Our third hypothesis was that low PaO<sub>2</sub>  
146 would predict a larger, negative mean effect size than moderate PaO<sub>2</sub>. This was based on the fact  
147 that the level for moderate hypoxia, which we designated for this study, might not induce  
148 feedback by the carotid body to the NTS (Virués-Ortega et al., 2004; West, 2004) and, hence,  
149 alter neurotransmitter activity in the brain. Finally, we hypothesized that hypobaric hypoxia  
150 would predict poorer cognitive functioning than during normobaric conditions. We also decided



151 to examine the possibility of an interaction effect between PaO<sub>2</sub> level and normobaric/hypobaric  
152 conditions.

## 153 2. Method

154 A systematic literature search, using the following data bases, Pubmed, SCOPUS,  
155 SportsDISCUS and Web of Knowledge, was undertaken. Each database was searched from their  
156 earliest available record up to September 2016. Key words used in the searches were  
157 combinations of “altitude”, “attention”, “central executive”, “cognition”, “hypobaric”,  
158 “hypoxia”, “learning”, “long-term memory”, “normobaric”, “perception”, “short-term memory”  
159 and “working memory”, In addition, reference lists from empirical reports and reviews were  
160 examined and screened for eligibility. Studies were included if they were performed on healthy  
161 humans; within-subject design was used; data were reported giving the PaO<sub>2</sub> or that allowed the  
162 PaO<sub>2</sub> to be estimated (e.g. arterial oxygen saturation and/or altitude); and the duration of being in  
163 a hypoxic state prior to cognitive testing was  $\leq 6$  days. Studies in which another independent  
164 variable was simultaneously administered to the participants (e.g. sleep deprivation) were not  
165 included although control conditions, which consisted of hypoxia alone, were included. English  
166 language restrictions were applied.

### 167 2.1. Selection of studies

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

### 172 2.2 Data extraction and management

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

### 177 2.3. Data analyses

178 A mixed effects model, with random effects to combine the studies within each subgroup  
179 of dependent variables (central executive tasks, perception/attention tasks and STM tasks) and  
180 fixed effects to combine subgroups to yield the main effect, was carried out. Study to study  
181 variance was not assumed to be the same and computed within subgroups not pooled across  
182 them. The moderators, moderate versus low PaO<sub>2</sub> level and normobaric versus hypobaric  
183 hypoxia, and the interaction between the two, were examined using meta-regression analyses  
184 (Borenstein et al., 2009). Publication bias was examined using Begg's test (Begg & Mazumdar,  
185 1994).

## 186 3. Results

### 187 3.1. Included studies.

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

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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

219           This is the first review to systematically examine the effect of acute hypoxia on central  
220 executive, perception/attention and STM tasks, and the effect of the moderating variables, low  
221 versus moderate PaO<sub>2</sub> and normobaric versus hypobaric conditions, and the interaction between  
222 the two variables. The results of this meta-analysis supply only limited support for our  
223 hypotheses. Firstly, as hypothesized, the main effect showed a moderate, negative mean effect  
224 size and is evidence for a significant, inhibitory effect of acute hypoxia on cognition. This  
225 supports the conclusions of the narrative reviewers (Taylor et al., 2016; Virués-Ortega et al.,  
226 2004), but the strength of the effect is greater than one might have expected from the probability-  
227 based results on which both sets of reviewers relied. Counterintuitively, however, we failed to  
228 support our hypothesis that central executive tasks would show higher, negative effect sizes  
229 compared to the non-executive tasks, i.e. perception/attention and STM tasks. Our hypothesis  
230 that low PaO<sub>2</sub> would predict a larger, negative mean effect size than moderate hypoxia was  
231 supported. Finally, the findings examining the use of normobaric versus hypobaric conditions are  
232 less transparent. Normobaric conditions predict poorer performance, with a moderate R<sup>2</sup> (.29),  
233 while the interaction with PaO<sub>2</sub> accounted for much more of the variation (R<sup>2</sup> = .45). This is only  
234 2% lower than the variation accounted for by PaO<sub>2</sub> alone, therefore showing that it is PaO<sub>2</sub> that  
235 significantly accounts for the results.

236           That the main mean effect size was only moderate is not surprising when one takes into  
237 account the fact that this included studies where cognition was tested at both moderate (61  
238 mmHg to 89 mmHg) and low (< 60 mmHg) levels of PaO<sub>2</sub>. The cut-off level for low PaO<sub>2</sub>, in  
239 this study, was set at a measure which is about the level at which physiological studies have  
240 shown the initiation of a response by the carotid body to the lowering of PaO<sub>2</sub> (Feldman et al.,  
241 .2013; West, 2004). In other words, in humans and other animals, it is not until this threshold is

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

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

265 also demonstrated this (Arnsten, 2009; 2011), we failed to show any significant differences in  
266 mean effect sizes between task types. Before examining these results in more detail, we will  
267 outline the differences between the tasks. Central executive tasks are part of what Baddeley  
268 (1986) termed working memory. According to Baddeley, working memory consists of three  
269 separate but inter-dependent parts, the central executive mechanism, and two STM systems, the  
270 phonological loop and the visuospatial sketch pad. The phonological loop is responsible for the  
271 encoding of acoustic and verbal information. The visuospatial sketchpad has the same role as the  
272 phonological loop except that it processes visual and visuospatial information. The role of the  
273 central executive is to integrate the perceptual input and compare the present situation (held in  
274 STM) with recalled information from long-term memory. Miyake et al. (2000) described the  
275 central executive process as involving several functions, which include shifting between tasks or  
276 mental sets; updating and monitoring working memory representations, which involves the  
277 removal of redundant information and replacing it with new, relevant information; inhibition of  
278 prepotent responses; planning; and the coordination of multiple tasks. Leh et al. (2010) provided  
279 other examples, e.g. abstract thinking, cognitive flexibility and selecting relevant sensory  
280 information. Positron Emission Tomography and functional Magnetic Resonance Imaging  
281 research has shown that central executive tasks primarily activate the prefrontal cortex (PFC) but  
282 also draw on information recalled from other parts of the brain (see Barbas, 2000; Leh et al.,  
283 2010, for reviews).

284 Perception/attention tasks are as those tasks which require focusing on and/or identifying  
285 relevant stimuli then carrying out a comparatively simple, pre-determined response (McMorris,  
286 2016). These are tasks such as simple and choice reaction time, visual search and coincidence  
287 anticipation. In general, the first stage of such tasks requires activation of the specific sensory

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

297         Our reasons for expecting differences in effects of hypoxia on the different task types was  
298 not based solely on empirical data and narrative reviews but also had a theoretical base. During  
299 stress, these tasks are greatly affected by the activity of the neurotransmitters dopamine (DA),  
300 NE and 5-hydroxytryptamine (5-HT: also known as serotonin), the peptide corticotropin  
301 releasing factor (CRF), and the hormones adrenocorticotrophin hormone (ACTH) and cortisol.  
302 Moreover, animal studies have shown that during hypoxia, feedback from chemoreceptors in the  
303 carotid body stimulate catecholaminergic and serotonergic neurons in the NTS (Chen et al.,  
304 2000; Wang & Fitzgerald, 2002), while CRF, ACTH and cortisol are synthesized and released  
305 from the hypothalamic-pituitary-adrenal (HPA) axis, modulated by the action of NE and its  
306 receptors in the paraventricular nucleus of the hypothalamus (Chen et al., 2004). Research with  
307 animals and humans has shown that during high levels of stress of any kind, NE in the LC is  
308 synthesized and released to other parts of the brain. Moreover, LC neurons also project to the  
309 ventral tegmental area (VTA), where they activate  $\alpha_1$ -adrenoceptors, which induce enhanced  
310 glutamate release thus potentiating the firing of DA neurons (Mejías-Aponte et al., 2009). High

311 concentrations of NE activate the low affinity  $\alpha_1$ - and  $\beta$ -adrenoceptors (Arnsten, 2011) in the  
312 PFC. Furthermore, within the PFC, glucocorticoids further stimulate activation of  $\alpha_1$ -  
313 adrenoceptors and D<sub>1</sub>-receptors (Shansky & Lipps, 2013). The activation of  $\alpha_1$ -adrenoceptors  
314 reduces neuronal firing, while increased stimulation of D<sub>1</sub>-receptors and  $\beta$ -adrenoceptors induces  
315 even greater activity of the second messenger, cyclic adenosine monophosphate, which dampens  
316 all neuronal activity, thus weakening the signal to ‘noise’ ratio (Arnsten, 2011). Hence, we  
317 expected to see cognitive performance of central executive tasks inhibited, as they require  
318 activation of the PFC.

319         Stress research with animals has shown that the situation with regard to non-executive  
320 tasks, which rely on activation of the sensory cortices and their association areas, is different.  
321 High concentrations of NE activating  $\alpha_1$ - and  $\beta$ -adrenoceptors can positively affect signal  
322 detection (Waterhouse et al., 1980; 1981). Moreover, research has also shown that this can be  
323 increased by CRF and 5-HT stimulation of the LC-NE system. CRF causes tonic firing of LC-  
324 NE neurons, which results in suppression of somatosensory signal transmission within the  
325 somatosensory thalamus and cortex (Devilbiss et al., 2012). This appears to reduce detectability  
326 of low-intensity stimuli without affecting high-intensity stimuli (Devilbiss & Waterhouse 2002;  
327 Moore, 2004). Arnsten (2009) saw this as a defense mechanism by which the organism increases  
328 its ability to detect high priority, dangerous stimuli and allows it to ignore non-threatening  
329 stimuli. Therefore, we thought that it was possible that such tasks, particularly  
330 perception/attention tasks, might be facilitated by low oxygen levels or, at least, unaffected.  
331 However, our results failed to support this, with no significant differences between tasks.

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



334 glucocorticoids and 5-HT in the brain (Chen et al., 2000; Erickson & Millhorn, 1984), which  
335 should result in facilitation of non-executive tasks in the manner explained in the previous  
336 paragraph. However, all task types were inhibited, with no significant differences between them.  
337 Our findings are probably best explained by the work of Gibson and colleagues (Gibson et al.,  
338 1981; Gibson & Peterson, 1982). They claimed that although animal and human studies have  
339 shown that during hypoxia, brain concentrations of DA and NE are not reduced, turnover most  
340 likely is. The fall in turnover appears to be due to the requirement for oxygen during the  
341 synthesis, release and metabolism of the catecholamine and serotonin neurotransmitters (Davis &  
342 Carlsson, 1973; Gibson et al., 1981; Gibson & Peterson, 1982; Shukitt-Hale et al., 1993). As a  
343 result, during low levels of oxygen, poor performance of all cognitive tasks is due to a lack of  
344 activity by DA, NE and 5-HT. This would have the same effect as low catecholamines and 5-HT  
345 concentrations in the brain which, in line with inverted-U theory (Yerkes & Dodson, 1908), is  
346 thought to inhibit performance of all types of task (Cooper, 1973; Decamp & Schneider, 2009;  
347 Kumar et al., 2011). When neurotransmitter concentrations are low, the appropriate sequence of  
348 neuronal activation cannot be obtained as a result of neurons being at such a low level of  
349 excitation that they cannot be stimulated to an adequate level of summation.

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

357 resulting in greater oxidative stress than in the normobaric condition (Faiss et al., 2013;  
358 Hemmingsson & Linnarsson, 2009). However, our data would strongly suggest that when  
359 determining the effect of hypoxia on cognition, PaO<sub>2</sub> level is the key factor, regardless of  
360 whether it is in hypobaric or normobaric conditions.

#### 361 4.1. Limitations

362 The conclusions of the current review are only applicable when PaO<sub>2</sub> levels range from  
363 89 mmHg to 35 mmHg and for a duration of 10 mins to 5 days. When PaO<sub>2</sub> is at very low levels,  
364 e.g. those found near the summit of Mount Everest (PaO<sub>2</sub> < 30 mmHg; West, 2004), cognition  
365 becomes severely inhibited (Wagner, 2010). Currently, there is significant debate regarding the  
366 effects of acclimatization on cognition (Malle et al., 2016; Rimoldi et al., 2016) and we  
367 considered this topic outside the scope of the current review. We should note however that the  
368 effects of acclimatization may be associated to the action of the transcription factor, hypoxia-  
369 inducible factor (HIF), which binds with hypoxia response element (HRE), to upregulate  
370 production of erythropoietin, angiogenic factors and glucose transporters (Bruick, 2003), which  
371 may help consolidate cognition.

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

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

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

## 389 5. Conclusion

390 In conclusion, the key findings to emerge from this this review are a) hypoxia has a  
391 negative effect on cognition, b) this is regardless of whether the task is central executive or a  
392 non-executive perception/attention or STM task, and c) it is likely that PaO<sub>2</sub> level, and not  
393 whether the exposure is in hypobaric hypoxic or normobaric hypoxic conditions, is the key  
394 predictor of cognitive performance.

395

## 396 6. References

397 \* Included in meta-analyses

398

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638

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

Experiment							
2							
Shukitt- Hale et al. (1998)	23	57 mmHg: 61 mmHg	normobaric	Tower of London <sup>b</sup> choice reaction time <sup>c</sup> simple reaction time <sup>c</sup> attention tasks <sup>c</sup>	-0.10 (0.05) <sup>f</sup> -0.43 (0.25) <sup>g</sup>	-0.19 -0.91	-0.002 0.06
Wu et al. (1998)	16	66 mmHg: 60 mmHg: 54 mmHg	normobaric	simple mathematics <sup>c</sup>	-0.89 (0.11)	-1.11	-0.69
Bonnon et al. (1999)	7	67 mmHg: 51 mmHg	hypobaric	attention task <sup>c</sup>	-0.44 (0.23)	-0.90	0.01
Singh et al. (2004)	20	70 mmHg: 61 mmHg	hypobaric	auditory oddball <sup>b</sup>	-0.23 (0.15)	-0.53	0.08
Pavlicek et al. (2005)	7	87 mmHg:	normobaric	word generation <sup>c</sup>	0.55 (0.87)	-1.15	2.25



Group 1		59 mmHg					
Pavlicek et al. (2005)	7	87 mmHg:	normobaric	word generation <sup>c</sup>	0.81 (0.89)	-0.94	2.55
Group 2		72 mmHg					
Hayashi et al. (2005)	17	60 mmHg	normobaric	auditory oddball <sup>b</sup>	-0.50 (0.07)	-0.63	-0.37
Tsarouchas et al. (2008)	10	58 mmHg	normobaric	go/no go <sup>b</sup>	-0.41 (0.14)	-0.69	-0.14
Li et al. (2012)	54	63 mmHg	hypobaric	visual choice reaction time <sup>c</sup>	-0.65 (0.02) <sup>g</sup>	-0.68	-0.62
Group 1		auditory choice reaction time <sup>c</sup> pursuit aiming <sup>c</sup> forward digit recall <sup>d</sup>					
		backward digit recall <sup>d</sup> Benton visual retention test <sup>d</sup>					
Li et al. (2012)	51	63 mmHg	hypobaric	visual choice reaction time <sup>c</sup>	-0.29 (0.02) <sup>g</sup>	-0.32	-0.26
Group 2		auditory choice reaction time <sup>c</sup>					

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				pursuit aiming <sup>c</sup>			
				forward digit			
				recall <sup>d</sup>	-0.26		
				backward digit	(0.01) <sup>h</sup>	-0.28	-0.24
				recall <sup>d</sup>			
				Benton visual			
				retention test <sup>d</sup>			
Ando et al. (2013)	12	89	normobaric	go/no go <sup>a</sup>	-0.52 (0.06)	-0.63	-0.40
		mmHg:					
		75 mmHg					
Asmaro et al. (2013)	35	52	normobaric	Stroop color	-0.57	-0.64	-0.51
		mmHg:		test <sup>b</sup>	(0.03) <sup>f</sup>		
		37 mmHg		trail making B <sup>b</sup>			
				trail making A <sup>c</sup>	-3.61	-3.65	-3.57
				forward digit	(0.02) <sup>g</sup>		
				recall <sup>d</sup>	-1.66	-1.71	-1.61
				backward digit	(0.03) <sup>h</sup>		
				recall <sup>d</sup>			
Stepanek et al. (2013)	25	40 mmHg	normobaric	King-Devick test <sup>c</sup>	-1.13 (0.02)	-1.17	-1.07
Zhang et al.	46	65 mmHg	hypobaric	choice reaction	-0.34	-0.37	-0.32

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(2013)				time <sup>c</sup>	(0.01) <sup>g</sup>		
				pursuit aiming <sup>c</sup>			
				forward digit			
				recall <sup>d</sup>	-0.25	-0.27	-0.23
				backward digit	(0.01) <sup>h</sup>		
				recall <sup>d</sup>			
				Benton visual			
				retention <sup>d</sup>			
Stepanek et al. (2014)	25	35	normobaric	King-Devick test <sup>c</sup>	-0.71	-0.76	-0.64
		mmHg:			(0.04)		
		40 mmHg					
Komiyama et al. (2015)	16	75 mmHg	normobaric	go/no go <sup>b</sup>	-0.64	-1.34	0.05
				spatial delay	(0.35) <sup>f</sup>		
				response <sup>d</sup>	0.10	-0.57	0.78
					(0.35) <sup>h</sup>		

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642 Note. <sup>a</sup> PaO<sub>2</sub> (arterial partial pressure of oxygen) was estimated from actual altitude, estimated  
643 altitude equivalent or mean oxygen saturation, hence values are only approximate.

644 <sup>b</sup> central executive task

645 <sup>c</sup> perception/attention task

646 <sup>d</sup> short-term memory task

647 <sup>e</sup> SE standard error

- 648 <sup>f</sup> g for central executive tasks
- 649 <sup>g</sup> g for perception/attention tasks
- 650 <sup>h</sup> g for short-term memory tasks
- 651 <sup>i</sup> CI confidence interval
- 652