

1 **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 (PaO₂) 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 PaO₂ or that allowed the PaO₂ 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. 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) PaO₂ 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

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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 (≤ 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 PaO₂ resulting in greater inhibition of performance than more moderate levels
93 of PaO₂ (readers not familiar with PaO₂ should note that lower PaO₂ means a greater negative
94 effect of hypoxia than moderate levels of PaO₂). 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 PaO₂ 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 PaO₂ 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 PaO₂
146 would predict a larger, negative mean effect size than moderate PaO₂. 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 (Virus-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 PaO₂ 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 PaO₂ or that allowed the
162 PaO₂ 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 ≤ 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 authors
170 were retrieved. Based on the information within the full reports, we used a standardized form to
171 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 PaO₂ 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 PaO₂ 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 PaO₂ 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 R² (.29),
233 while the interaction with PaO₂ accounted for much more of the variation (R² = .45). This is only
234 2% lower than the variation accounted for by PaO₂ alone, therefore showing that it is PaO₂ 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 PaO₂. The cut-off level for low PaO₂, 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 PaO₂ (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 PaO₂ levels.
245 The B coefficient (0.81) and moderate to high R² (.47) show that PaO₂ level is a strong predictor
246 of deterioration in cognitive performance, with performance weaker at low levels of PaO₂. This
247 suggests that when PaO₂ 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 PaO₂, 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 α_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 α_1 - and β -adrenoceptors (Arnsten, 2011) in the
312 PFC. Furthermore, within the PFC, glucocorticoids further stimulate activation of α_1 -
313 adrenoceptors and D₁-receptors (Shansky & Lipps, 2013). The activation of α_1 -adrenoceptors
314 reduces neuronal firing, while increased stimulation of D₁-receptors and β -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 α_1 - and β -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_2 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, PaO₂ 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 PaO₂ levels range from
363 89 mmHg to 35 mmHg and for a duration of 10 mins to 5 days. When PaO₂ is at very low levels,
364 e.g. those found near the summit of Mount Everest (PaO₂ < 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 PaO₂ 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

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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 ₂ ^a	Normobaric or hypobaric	Cognitive task	Hedges'	95% CI ^f interval	
					g (SE ^e)	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-	23	57	normobaric	Tower of	-0.10	-0.19	-0.002
Hale et al.		mmHg:		London ^b	(0.05) ^f		
(1998)		61 mmHg		choice reaction			
				time ^c	-0.43		
				simple reaction	(0.25) ^g	-0.91	0.06
				time ^c			
				attention tasks ^c			
Wu et al.	16	66	normobaric	simple	-0.89	-1.11	-0.69
(1998)		mmHg:		mathematics ^c	(0.11)		
		60					
		mmHg:					
		54 mmHg					
Bonnon et	7	67	hypobaric	attention task ^c	-0.44	-0.90	0.01
al. (1999)		mmHg:			(0.23)		
		51 mmHg					
Singh et al.	20	70	hypobaric	auditory	-0.23	-0.53	0.08
(2004)		mmHg:		oddball ^b	(0.15)		
		61 mmHg					

Pavlicek et al. (2005)	7	87 mmHg:	normobaric	word generation ^c	0.55 (0.87)	-1.15	2.25
Group 1		59 mmHg					
Pavlicek et al. (2005)	7	87 mmHg:	normobaric	word generation ^c	0.81 (0.89)	-0.94	2.55
Group 2		72 mmHg					
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)	54	63 mmHg	hypobaric	visual choice			
Group 1				reaction time ^c	-0.65 (0.02) ^g	-0.68	-0.62
				auditory choice			
				reaction time ^c			
				pursuit aiming ^c			
				forward digit			
				recall ^d	-0.24 (0.01) ^h	-0.26	-0.23
				backward digit			
				recall ^d			
				Benton visual retention test ^d			
Li et al. (2012)	51	63 mmHg	hypobaric	visual choice			
				reaction time ^c		-0.32	-0.26

Group 2				auditory choice	-0.29		
				reaction time ^c	(0.02) ^g		
				pursuit aiming ^c			
				forward digit			
				recall ^d			
				backward digit	-0.26	-0.28	-0.24
				recall ^d	(0.01) ^h		
				Benton visual			
				retention test ^d			
Ando et al. (2013)	12	89	normobaric	go/no go ^a	-0.52 (0.06)	-0.63	-0.40
				mmHg:			
				75 mmHg			
Asmaro et al. (2013)	35	52	normobaric	Stroop color	-0.57 (0.03) ^f	-0.64	-0.51
				test ^b			
				37 mmHg			
				trail making B ^b			
				trail making A ^c	-3.61	-3.65	-3.57
				forward digit	(0.02) ^g		
				recall ^d	-1.66	-1.71	-1.61
				backward digit	(0.03) ^h		
				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 PaO₂ (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

645 ^c perception/attention task

646 ^d short-term memory task

647 ^e SE standard error

648 ^f g for central executive tasks

649 ^g g for perception/attention tasks

650 ^h g for short-term memory tasks

651 ⁱ CI confidence interval

652