A systematic review of electroencephalography in acute cerebral hypoxia: clinical and diving implications

Nicole YE Wong[1,2], Hanna van Waart[1], Jamie W Sleigh[1,3], Simon J Mitchell[1,2,4], Xavier CE Vrijdag[1]

[1] *Department of Anaesthesiology, University of Auckland, Auckland, New Zealand*
[2] *Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand*
[3] *Department of Anaesthesia, Waikato Hospital, Hamilton, New Zealand*
[4] *Slark Hyperbaric Unit, North Shore Hospital, Auckland, New Zealand*

Corresponding author: *Dr Xavier CE Vrijdag, Department of Anaesthesiology, School of Medicine, University of Auckland, Private bag 92019, Auckland 1142, New Zealand*
ORCiD: 0000-0001-5907-6083
x.vrijdag@auckland.ac.nz

Keywords
Diving research; Diving safety memos; Physiology; Neurology; Brain

Abstract
(Wong NYE, van Waart H, Sleigh JW, Mitchell SJ, Vrijdag XCE. A systematic review of electroencephalography in acute cerebral hypoxia: clinical and diving implications. Diving and Hyperbaric Medicine. 2023 September 30;53(3):268–280. doi: 10.28920/dhm53.3.268-280. PMID: 37718302.)
Introduction: Hypoxia can cause central nervous system dysfunction and injury. Hypoxia is a particular risk during rebreather diving. Given its subtle symptom profile and its catastrophic consequences there is a need for reliable hypoxia monitoring. Electroencephalography (EEG) is being investigated as a real time monitor for multiple diving problems related to inspired gas, including hypoxia.
Methods: A systematic literature search identified articles investigating the relationship between EEG changes and acute cerebral hypoxia in healthy adults. Quality of clinical evidence was assessed using the Newcastle-Ottawa scale.
Results: Eighty-one studies were included for analysis. Only one study investigated divers. Twelve studies described quantitative EEG spectral power differences. Moderate hypoxia tended to result in increased alpha activity. With severe hypoxia, alpha activity decreased whilst delta and theta activities increased. However, since studies that utilised cognitive testing during the hypoxic exposure more frequently reported opposite results it appears cognitive processing might mask hypoxic EEG changes. Other analysis techniques (evoked potentials and electrical equivalents of dipole signals), demonstrated sustained regulation of autonomic responses despite worsening hypoxia. Other studies utilised quantitative EEG analysis techniques, (Bispectral index [BIS™], approximate entropy and Lempel-Ziv complexity). No change was reported in BIS™ value, whilst an increase in approximate entropy and Lempel-Ziv complexity occurred with worsening hypoxia.
Conclusions: Electroencephalographic frequency patterns change in response to acute cerebral hypoxia. There is paucity of literature on the relationship between quantitative EEG analysis techniques and cerebral hypoxia. Because of the conflicting results in EEG power frequency analysis, future research needs to quantitatively define a hypoxia-EEG response curve, and how it is altered by concurrent cognitive task loading.

Introduction

Comprehensively understanding how hypoxia affects the brain will not only benefit clinicians managing cerebral hypoxia in the context of trauma, neurosurgery or anaesthesia, but will also benefit divers. Unanticipated severe hypoxia can occur in divers due to failure of close circuit rebreather devices resulting in rebreathing of a hypoxic gas mixture, or open circuit divers breathing the wrong gas mixture at the wrong depth.[1]

The central nervous system is highly susceptible to hypoxia.[2] An interruption in cerebral blood flow or impaired oxygenation of arterial blood can reduce oxygen availability and failure to meet the demands of the central nervous system. This can result in transient or permanent neurological symptoms.[3] Symptoms associated with mild cerebral hypoxia include difficulties with complex learning tasks, inattention, and amnesia.[4] In moderate cerebral hypoxia, reduced motor co-ordination, and impaired higher-order cognitive functions can arise.[4] In severe cerebral hypoxia, syncope, seizure and neurological death can ultimately result.[4] It is notable that humans appear to have a poor appreciation of hypoxia symptoms as they develop, reducing the chance of recognition and self-rescue.

Given the importance of recognising and reversing hypoxia whilst diving, there is a need for an improved method of hypoxia detection. One proposed method is through the use of electroencephalography (EEG); a promising indicator of

hypoxia with the advantages of being non-invasive, sensitive, objective and measuring in real-time.[5]

Electroencephalography provides a graphical representation of potential differences between cerebral locations.[6] The most frequently used method for classifying EEG waveforms is by frequency. Alpha waves (8–12 Hz) are present in normal awake EEG recordings and are an indication of relaxed wakefulness. Alterations to alpha waves are considered a sign of generalised cerebral dysfunction.[7] Beta waves (13–30 Hz) can increase in the frontal region at low amplitude during active thinking, focus and concentration.[8] Delta waves (< 4 Hz) physiologically occur in deep sleep, and can pathologically occur with focal cerebral dysfunction.[7] Theta waves (4–7 Hz) are present in states of drowsiness and early stages of sleep.[7]

In the last decade, technological advancements have allowed continuous EEG monitoring in clinical practice to be more feasible. Difficulties associated with continuous EEG monitoring are more logistical in nature, such as difficult electrode maintenance, lack of effective computer algorithms and lack of clinical expertise for interpretation.[9] Quantitative EEG analysis techniques, such as bispectral index (BIS™), approximate entropy and Lempel-Ziv complexity utilise advances in computer power and algorithms to allow continuous monitoring of cerebral function, particularly in intensive care and anaesthesia.[9] In theory, the use of continuous EEG in the clinical environment could translate into underwater use, employing algorithms that successfully detect hypoxia. Our group is currently engaged in a program to investigate the utility of multipurpose EEG algorithms for detecting adverse gas effects during diving such as nitrogen narcosis, hypoxia, hyperoxia and hypercapnia.

The objective of this systematic review was to explore and critically analyse the current literature investigating the relationship between EEG changes and acute cerebral hypoxia in healthy adults. Having an in-depth understanding of how EEG is affected by acute cerebral hypoxia could contribute towards the development of future technology to monitor and reduce the risk of fatal cerebral hypoxic events occurring clinically and during diving.

Methods

SEARCH STRATEGY

A systematic electronic search was performed in MEDLINE, EMBASE, Scopus and Web of Science on 12 April 2021. The search term was drafted with the assistance of a University of Auckland librarian, resulting in this MEDLINE search string: ((Electroencephalography/ OR (eeg or eegs or electroencephalogra*).ti,ab,kw,kf.) AND (Hypoxia/ OR Hypoxia, Brain/ OR (hypoxi* or hypox?em*).ti,ab,kw,kf. OR (anoxi* or anox?e*).ti,ab,kw,kf. OR (oxygen adj2 deficien*).ti,ab,kw,kf. OR Altitude/ OR altitude?.ti,ab,kw,kf.)) not (exp animals/ not humans.sh.)

The MEDLINE search string was translated into formats compatible with the other three databases with the aid of a Polyglot webtool and cross-checked by the university librarian.

STUDY SELECTION

Search results from all four databases were exported to a reference managing database (Covidence, Melbourne, Australia) for de-duplication and review. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed.[19] All non-English language articles were translated for the screening and review process. Three reviewers (NW, XV, HvW) independently screened all titles and abstracts in double and excluded irrelevant studies. No date or language limits were set. Exclusion criteria included systematic reviews, meta-analyses, letters, editorials, case reports, paediatric studies, animal studies or studies investigating participants with pathologies. Any disagreements over inclusion or exclusion of studies were discussed between the three reviewers to reach consensus.

Full text copies of all potentially relevant studies were obtained for review. In addition to the exclusion criteria utilised for title and abstract screening, full-text studies were excluded if some index of the hypoxic severity was not described (i.e., inspired partial pressure of oxygen [PiO_2] or peripheral oxygen saturation [SpO_2] were not stated), or if there was no clear qualitative or quantitative description of EEG outcomes. Additional studies were retrieved by liaising with content experts (senior anaesthetists and research professors) to contribute any relevant grey literature that was not captured by our search strings. Reference lists of all included full-text studies were also manually reviewed for additional relevant publications (literature snowballing).

DATA EXTRACTION

Data extraction was performed by NW and XV and entered into a pre-designed electronic table. Data extracted included: participant demographics, study design, extent of hypoxia achieved, EEG results and analysis. The quantitative data extracted was too varied to reliably perform a formal meta-analysis.

QUALITY OF EVIDENCE

The Newcastle-Ottawa scale was applied to assess quality of evidence. This scale assesses the methodological quality of: cohort selection (4 points), comparability of the study groups (2 points), and quality of outcomes assessed (3 points).[10] Cohort selection is determined by the representativeness of the exposed cohort to the target population, how the non-exposed cohort is selected, the ascertainment of the exposure, and demonstration that the outcome of interest was not present at the start of the study. Study group comparability is based on whether the study controls for potentially confounding factors (such as age and gender).

Quality of outcomes assessed is based on whether there was independent blind assessment of outcomes, whether sufficient time was allowed for outcomes to occur, and the adequacy of follow-up of cohorts. A score is formulated out of a maximum of nine points. The thresholds for converting the Newcastle-Ottawa scale into an objective assessment of study quality (as per the Agency for Healthcare Research Quality standards) is as follows:

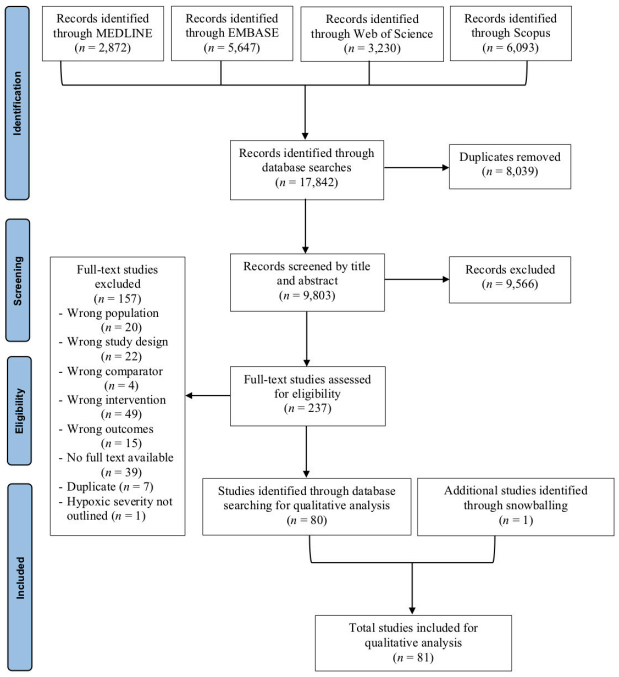
- Good quality – 3 or 4 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in assessed outcome domain.
- Fair quality – 2 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in assessed outcome domain.
- Poor quality – 0 or 1 point in selection domain OR 0 points in comparability domain OR 0 or 1 points in assessed outcome domain.

Results

STUDIES INCLUDED FOR ANALYSIS

The search identified 17,842 records, with 9,803 remaining for title and abstract screening after duplicates were removed. After initial screening, 237 full-text studies were assessed for eligibility. Eighty studies met the inclusion criteria. One study was identified through snowballing, resulting in 81 studies for analysis (Figure 1). A complete list of these studies can be found in online supplementary Table S1*.

Figure 1
PRISMA flow diagram for the review



QUALITY OF EVIDENCE

The overall quality of evidence was poor. Only ten studies were graded as being of good quality. The comparability domain scored the worst, where more than 80% of studies scored no points (Table 1).

TYPE OF STUDIES

Thirteen controlled trials were identified, which involved randomisation to another intervention. The remaining studies identified were experimental cohort studies.

STUDY PARTICIPANTS

The majority of studies were very small, with less than 20 participants recruited. The greatest number of participants (n = 203) were recruited in an experimental cohort study that investigated the tolerance time to hypoxia in trainee pilots at progressively increasing altitudes simulated in a hypobaric chamber.[11] Only four studies recruited more females than males. The majority of participants were under 40 years of age, with the oldest participant aged 57.[12] All participants were healthy volunteers who were naïve to hypoxic or altitude exposure. In particular, three studies recruited athletes,[13–15] one study recruited divers,[16] and six studies recruited pilots, parachutists or mountaineers (Table 2).[11,17–21]

MODERATE VS SEVERE HYPOXIA

Seventeen studies investigated more than one hypoxic exposure (nine studies investigated two exposures; six studies investigated three exposures; two studies investigated four exposures), producing a total of 108 exposures for analysis. The 108 exposures were categorised into two groups for comparison: moderate and severe hypoxia. Moderate hypoxia was defined as SpO_2 75–90% and severe hypoxia was defined as SpO_2 < 75%. For studies that did not state an SpO_2 outcome, severity of hypoxia was categorised based on PiO_2 exposure as a secondary outcome. In these studies, moderate hypoxia was defined as PiO_2 ≥ 10 kPa and severe hypoxia was defined as PiO_2 < 10 kPa. This categorisation produced 48 moderate hypoxia exposures and 60 severe hypoxia exposures for analysis and comparison.

INDUCTION OF HYPOXIA

Hypoxia was induced in a hypobaric chamber or an altitude exposure, or via normobaric hypoxia (inhalation of a hypoxic gas mixture). The most prevalent method of inducing moderate hypoxia was in a hypobaric chamber, whilst the most prevalent method of inducing severe hypoxia was via an inhaled hypoxic gas mixture. All altitude exposures produced a moderately hypoxic environment (Figure 2).

Footnote: * Table S1 in spreadsheet format is available on DHM Journal's website: https://dhmjournal.com/images/HTML/Wong_TableS1.htm. A table of the references cited in S1 is also available: https://www.dhmjournal.com/index.php/journals?id=320

Table 1

Newcastle-Ottawa scale quality of evidence; [a] Selection domain maximum 4 points; [b] Comparability domain maximum 2 points; [c] Assessed outcome domain maximum 3 points; N/A – Not applicable

Score	Selection [a]	Comparability [b]	Assessed outcome [c]
≥ 3 points	26	N/A	55
2 points	40	0	22
1 point	15	15	4
0 points	0	66	0
Overall assessment	**Good**	**Fair**	**Poor**
Number of studies	10	5	66

Table 2

Study participant characteristics

Parameter	*n* studies
***n* subjects**	
< 10	14
10–19	35
20–29	11
30–39	7
40–49	5
≥ 50	9
Male	
100%	39
50–99%	24
< 50%	4
Not stated	14
Upper age (years)	
18–19	1
20–29	17
30–39	24
40–49	14
50–59	6
Not stated	19
Characteristic	
Unspecified healthy volunteers	60
Students	9
Athletes	3
Divers	1
Pilots/parachutists/ mountaineers	6
Not stated	2

Figure 2

Methods of inducing hypoxia employed in the studies

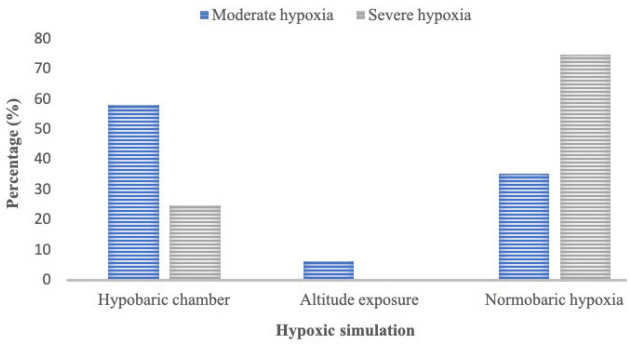
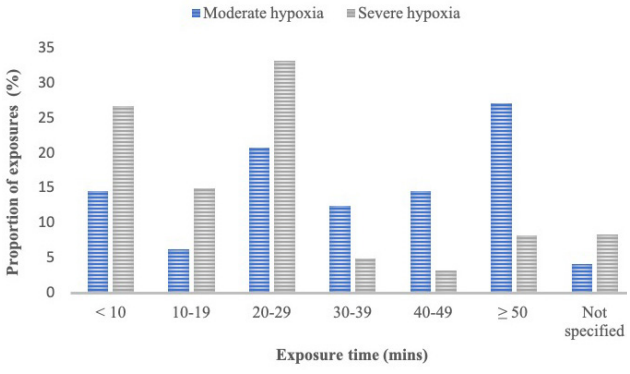


Figure 3

Hypoxia exposure times employed in the studies



EXPOSURE TIME

Hypoxic exposures were more frequently longer in the moderate hypoxia group, with the longest hypoxic exposure being 30 days secondary to ascent to higher altitude.[22] This is in contrast to the higher proportion of short exposures in the severe hypoxia group, where the shortest exposure was 12 seconds in a hypobaric chamber (Figure 3).[23]

EEG FREQUENCY ANALYSIS

Only 12 studies reported numerical changes in spectral power of EEG frequencies (Table 3). The remaining studies provided either written descriptions or graphs showing general trends in EEG frequency changes, from which specific numerical values could not be accurately ascertained.

Table 3

Experimental cohort studies that reported numerical changes in spectral power of EEG frequencies (n = 12); reference 31 was a randomised controlled trial. Reference 13 specifically recruited athletes, swimmers and skiers. Participants in all studies were described as healthy volunteers. FiO_2 – fraction of inspired oxygen; PiO_2 – pressure of inspired oxygen; SpO_2 – peripheral oxygen saturation EEG - electroencephalography

Study		Participant demographics			Study design						% change in EEG spectral power			
Ref	Year	*n*	Gender	Age range	Induction of hypoxia	Exposure (mins)	FiO_2 (%)	PiO_2 (kPa)	SpO_2 (%)	Hypoxia classification	Alpha	Beta	Delta	Theta
13	2012	24	100% Male	18–26	Inhaled hypoxic gas mixture	25	10	9.5	74	Severe	-29.4			+5.2
24	2020	12	100% Male		Inhaled hypoxic gas mixture	25	8	7.6		Severe	+30.9		+302.7	+287.4
25	2020	12	100% Male	20–25	Inhaled hypoxic gas mixture	600	12	11.4		Moderate	+31.0			+29.6
26	2005	10	50% Male; 50% Female	26–57	Brought to higher altitude	6	21	14		Moderate	+15.0	+30.0		
27	2008	10	100% Male	21–30	Hypobaric environment 4,000 m	6	21	11.6	83.8	Moderate	+46.1	+64.5		
28	1988	36	100% Male	18–27	Hypobaric environment	10	21	8.4	70	Severe	-20.6		+34.7	+17.3
29	2007	10	50% Male; 50% Female	21–41	Hypobaric environment 7,620 m, 6,096 m, 4,572 m	90	21	6.6, 8.5, 10.7		Severe at 7,620 m and 6,096 m; Moderate at 4,572 m	+22.2 (7,620 m) % change at other altitudes not stated			+23.8 (7,620 m) % change at other altitudes not stated
30	2003	3	33% Male; 67% Female	24–32	Rebreathing from a 5 L bag of room air	4.85	21		73	Severe	-40.5	-17.2		+16.5
31	1987	15	47% Male; 53% Female	21–41	Inhaled hypoxic gas mixture	23	9.8	9.3		Severe	-23.0	+157.1	+1.5	+1.5
32	1986	8	100% Male		Inhaled hypoxic gas mixture	20	10.5	9.98		Severe	-10.5	+15.5	-19.0	-9.0
22	2002	68	100% Male	18–19	Ascent to altitude – 3,600 m	43,200	21	12.3		Moderate	+56.9			+40.0
33	2002	12	67% Male; 33% Female	19–27	Inhaled hypoxic gas mixture	130			80	Moderate	-9.2		-3.6 at SpO_2 90%; % increase at SpO_2 80% not stated	-7.2 at SpO_2 90%; % increase at SpO_2 80% not stated

Table 4
Descriptive changes in EEG frequencies under moderate and severe hypoxic conditions; ↑ – Increased activity; ↓ – Decreased activity; ↔ – No change in activity

Hypoxic severity	Electroencephalogram frequency band															
	Alpha				Beta				Delta				Theta			
	↑	↓	↔	Not stated	↑	↓	↔	Not stated	↑	↓	↔	Not stated	↑	↓	↔	Not stated
Moderate (n = 48)	5	13	3	27	9	3	1	35	7	1	1	39	11	5	0	32
Severe (n = 60)	6	33	1	20	9	6	1	44	27	3	1	29	35	2	0	23

Table 5
Descriptive changes in EEG frequencies with cognitive testing compared to no cognitive testing under hypoxic conditions; ↑ – Increased activity; ↓ – Decreased activity; ↔ – No change in activity

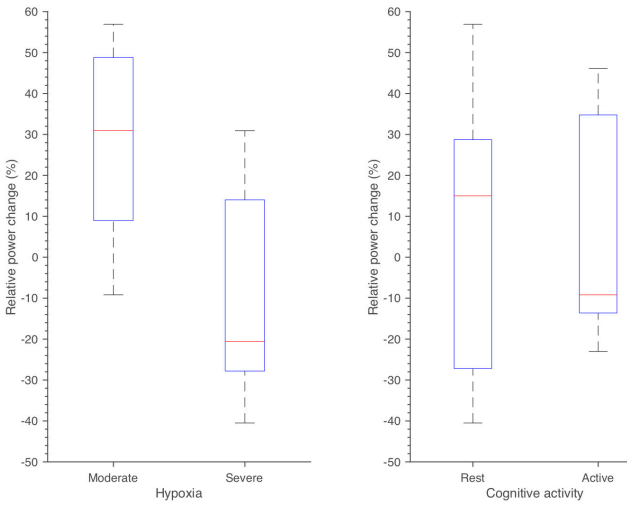
Cognitive testing	Electroencephalogram frequency band															
	Alpha				Beta				Delta				Theta			
	↑	↓	↔	Not stated	↑	↓	↔	Not stated	↑	↓	↔	Not stated	↑	↓	↔	Not stated
Yes (n = 34)	7	14	0	13	6	3	1	24	13	2	1	18	16	1	0	17
No (n = 74)	4	32	4	34	12	6	1	55	21	2	1	50	30	6	0	38

Alpha waves

Based on the 12 studies that specified numerical changes in spectral power of EEG frequencies, moderate hypoxia caused a 31% increase, compared to a 20.6% decrease in median alpha spectral power under severe hypoxic conditions (Figure 4). However, when including the qualitative studies, there appeared to be an overall decrease in alpha activity under both moderate and severe hypoxic exposures, where the decrease in alpha activity was more frequently reported under severe hypoxia compared to moderate hypoxia (Table 4). In general, the quantitative studies were more recent, with modern technology, while the studies with qualitative data were older, which mean that most results were based on visual interpretation of the EEG, which has severe limitations.

Amongst studies that reported an increase in alpha activity, a large proportion (seven out of 11) occurred in those where participants performed simple cognitive tasks during the hypoxic event, while 32 out of 46 showed a decrease in alpha power when no cognitive testing was performed (Table 5). This relationship is not depicted in Figure 4, which demonstrates a 15% increase in median alpha spectral power when no cognitive tasks were performed, and a 9.2% decrease in median alpha spectral power when cognitive tasks were performed under hypoxic conditions. However, only seven out of the 34 studies that utilised cognitive testing specified numerical changes in alpha spectral power.

Figure 4
Box plot of relative change in spectral power in the alpha band; study results are split between moderate and severe hypoxia (left) and rest or active cognitive function (right). The box plot shows the median (red line), interquartile range (blue box) and the whiskers show the range



Delta and Theta waves

Delta and theta waves generally increased under both moderate and severe hypoxic conditions (Table 4, Figures 5 and 6). The increase in delta activity under moderate

hypoxia is depicted as a red line without box and whiskers in Figure 5. This is because out of the seven studies that described an increase in delta activity under moderate hypoxia, only one study quantified these changes.[33] The authors of this study reported a 3.6% decrease in delta spectral power at SpO_2 90%, but an unspecified increase in delta spectral power at SpO_2 80%.[33]

The increase in both delta and theta activity was more frequently reported under severe hypoxic conditions (Table 4). More than 50% of studies did not report any changes in delta or theta activity, pertaining mainly to those that had a moderate hypoxic exposure. An increase in these frequencies was also more frequently reported in the absence of cognitive testing (Table 5), corresponding to 168.7% and 16.9% increases in median delta and theta spectral powers respectively, (Figures 5 and 6). Two studies noted an increase in theta activity predominantly over the frontal and parietal cortices.[22,34] One study reported a decrease in theta activity which was only observed over the frontal and central cortices.[35] Burykh, et al. demonstrated an increase in theta spectral power of 287.4%,[24] corresponding to the upper limit depicted in the severe hypoxia and resting state boxplots in Figure 6. Whilst this is a notable outlier, those authors investigated a small population and several EEG frequency changes were analysed by visual inspection.[24]

Beta waves

More than 70% of studies did not comment on nor specify any changes in beta activity. Studies that did generally reported an increase in beta spectral power for both moderate and severe hypoxic exposures (47.3% and 15.5%, respectively) (Table 4 and Figure 7). The majority of studies that utilised cognitive testing during the hypoxic event demonstrated an increase in beta activity (Table 5), which was also reflected by the 64.5% increase in median beta spectral power in studies that utilised cognitive testing during the hypoxic event (Figure 7).

OTHER EEG ANALYSIS TECHNIQUES

Nine studies utilised other analysis techniques rather than analysis of specific EEG frequencies (Table 6). These other analyses can be broadly categorised as evoked potentials, source localisation and quantitative analysis techniques.

Evoked potentials

Evoked potentials provide an insight into the processes underlying sensory load perception.[45] One study measured respiratory-related evoked potentials concluding that hypoxic conditions suppress respiratory afferent input to the medulla.[37] Three studies utilised auditory evoked potentials.[40,41,43] All three demonstrated a reduction in amplitude of endogenous positive and negative slow waves, corresponding to a disruption in focus, attention and auditory processing secondary to hypoxia.[40,41,43]

Source localisation

Electrical equivalents of dipole signals, which measure the electrical activity of subcortical regions,[42] were analysed

Figure 5

Box plot of relative change in spectral power in the delta band; study results are split between moderate and severe hypoxia (left) and rest or active cognitive function (right). The box plot shows the median (red line), interquartile range (blue box) and the whiskers show the range

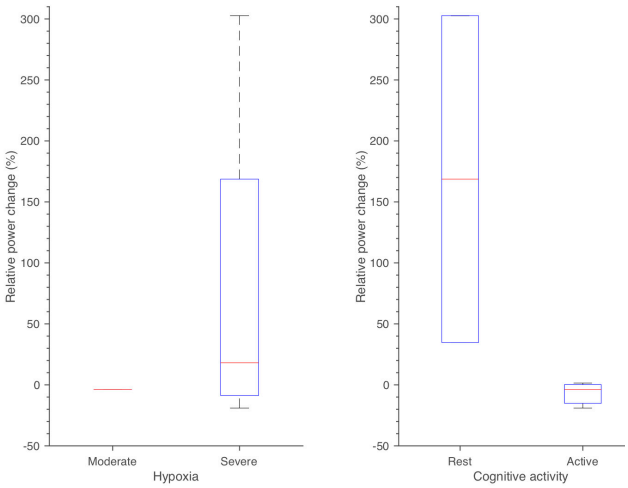


Figure 6

Box plot of relative change in spectral power in the theta band; study results are split between moderate and severe hypoxia (left) and rest or active cognitive function (right). The box plot shows the median (red line), interquartile range (blue box) and the whiskers show the range. The outlier (red +) is larger than 1.5 times the interquartile range and is outside the scale (dotted line) at 287.4%

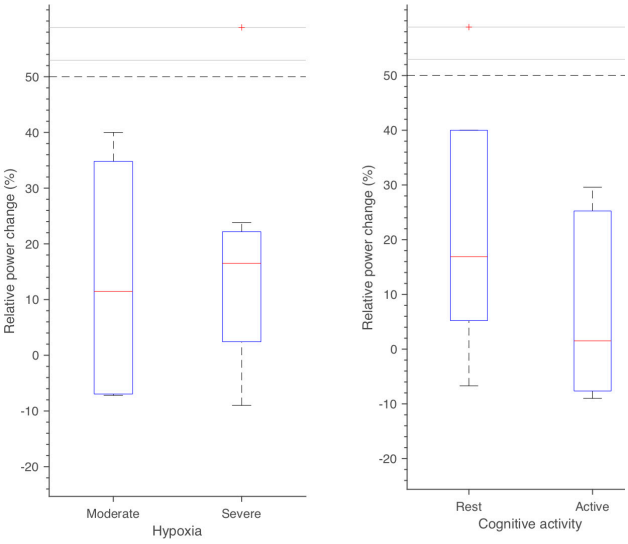
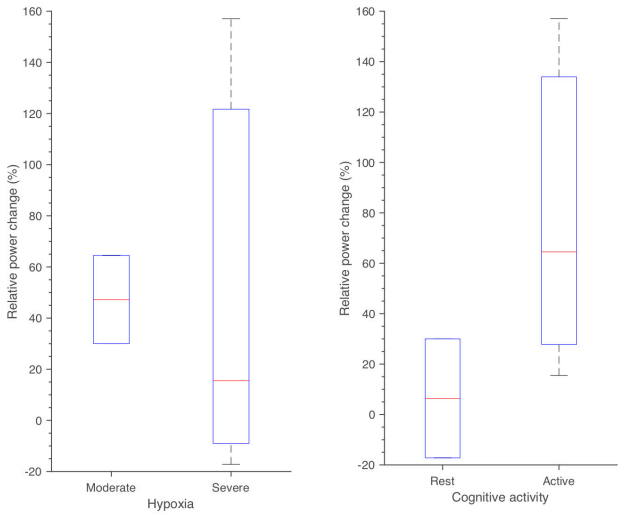


Figure 7
Box plot of relative change in spectral power in the beta band; study results are split between moderate and severe hypoxia (left) and rest or active cognitive function (right). The box plot shows the median (red line), interquartile range (blue box) and the whiskers show the range



in two studies.[42,44] Both demonstrated an increased signal density in the hypothalamus, forebrain, temporal lobe and increased activation of the limbic system with initial hypoxic exposure. The authors concluded that this signal redistribution demonstrates the dynamic adaptive functions and self-regulatory mechanisms of the brain, resulting in a stable regulation of physiological parameters despite a worsening oxygen deficit.[42,44]

Quantitative analysis techniques

Bispectral index (BIS™) is a proprietary signal-processed EEG that produces a single dimensionless number to provide an indication of depth of anaesthesia.[46] One study demonstrated no change in BIS™ across a range of SpO_2 readings from normal to as low as < 69%.[38]

Approximate entropy is a statistical approach to characterising EEG signals.[36] Lempel-Ziv complexity tests the randomness of a sequence to assess patterns within a deterministic, non-linear EEG signal.[36,39] One study utilised both approximate entropy and Lempel-Ziv complexity, showing a progressive increase in both values with worsening hypoxia.[36] The authors proposed that these methods can be used to evaluate changes in neurological function at different hypoxic severities.[36] These changes in complexity could be explained by the changes in beta frequency power reported earlier.

Discussion

This systematic review aimed to explore and critically analyse current literature investigating the relationship between EEG changes and acute cerebral hypoxia in healthy adults. There was evidence for EEG frequency changes associated with varying severities of hypoxic exposure although quantitative EEG analysis techniques have the greatest potential for evaluating the presence and severity of cerebral hypoxia.[6]

EEG FREQUENCY ANALYSIS

Alpha waves

Most studies in this systematic review reported changes in alpha waves. Under normal physiological conditions, alpha waves are associated with a state of relaxed wakefulness, where an alteration can be attributed to generalised cerebral dysfunction.[7] Overall, the reviewed studies confirmed a decrease in alpha wave activity under both moderate and severe hypoxic conditions (Table 4). One study reported that task difficulty and visual stimulus handling could affect alpha frequency amplitudes during continuous EEG monitoring.[47] Similarly, a large proportion of studies that reported an increase in alpha activity were those in which cognitive tasks were performed during the hypoxic exposure (Table 5). It is possible that there are other circumstances where alpha activity may also increase, and therefore cause an erroneous interpretation of an individual's hypoxic state.

Delta and Theta waves

Both delta and theta waves are physiologically associated with sleep.[7] It was therefore anticipated that these frequencies would increase during a hypoxic event and in the absence of cognitive testing, which aligns with the results of this systematic review (Tables 4 and 5). Nearly 50% of studies did not observe significant changes in delta or theta waves, whilst those that did, tended to observe an increase in delta and theta waves at severe hypoxic thresholds (Table 4). It is possible that these studies may also have other factors contributing to the observed increase in delta and theta waves. Whilst an increase in delta and theta activity may be a useful indicator of severe cerebral hypoxia, identification of earlier stages of cerebral hypoxia may be missed if relying on delta and theta waves alone.

Beta waves

More than 70% of studies did not comment on beta waves. The few studies that did, predominantly reported an increase in beta activity (Table 4). Beta waves are associated with active thinking, focus and concentration,[8] which aligns with the fact that the majority of studies where cognitive testing was utilised, reported an increase in beta activity (Table 5). Xi, et al. demonstrated that sedatives can also increase beta activity.[48] Like alpha waves, there may be other factors that could also contribute towards an increase in beta activity, resulting in an inaccurate interpretation of an individual's hypoxic state. This highlights the need for a more specific and reliable method of EEG analysis to monitor cerebral hypoxia.

Table 6

Experimental cohort studies that utilised other EEG analysis techniques ($n = 9$); reference 38 specifically recruited members of the defence force. Participants in all studies were described as healthy volunteers. BIS™ – Bispectral Index; EEG – electroencephalography; EEDS – Electrical equivalents of dipole signals; FiO_2 – fraction of inspired oxygen; PiO_2 – pressure of inspired oxygen; SpO_2 – peripheral oxygen saturation

Study		Participant demographics			Study design						Other EEG analysis techniques
Ref	Year	*n*	Gender	Age range	Induction of hypoxia	Exposure (mins)	FiO_2 (%)	PiO_2 (kPa)	SpO_2 (%)	Hypoxia classification	
36	2005	3	100% Male		Inhaled hypoxic gas mixture – 3,500 m	30	21	12.5		Moderate	Lempel-Ziv complexity and approximate entropy values increased with hypoxia
37	2005	11	55% Male; 45% Female		Inhaled hypoxic gas mixture	30	9	8.6	82.2	Moderate	Reduced P1 (32.4%) and P2 (20.2%) amplitudes (positive slow waves) of respiratory-related evoked potentials
38	2009	11	82% Male; 18% Female	20–46	Hypobaric environment – 7,620 m	5	21	6.6	69	Severe	No change in BIS™ value with a hypobaric hypoxia exposure (SpO_2 69%) compared to hypobaric normoxia and sea level exposures
39	2006	12	42% Male; 58% Female	26–32	Rebreathing from a 5 L bag of room air	7	21		75	Moderate	Lempel-Ziv complexity increased in subjects who experienced anxiety. No appreciable change in Lempel-Ziv complexity in subjects who were not anxious. EEG frequencies remained unchanged at SpO_2 75%
40	1993	38	100% Male	22–40	Hypobaric environment – 3,000 m, 4,000 m, 5,000 m, 6,000 m	45	21	12.8; 11.6; 10.0; 8.6	63.4 at 6,000 m	Moderate at 3,000 m, 4,000 m and 5,000 m; Severe at 6,000 m	Both negative and positive slow waves of auditory evoked potentials decreased in amplitude with increasing altitude
41	1975	10	100% Male	27–30	Inhaled hypoxic gas mixture	20	8	7.6		Severe	Decreased amplitude and latency of auditory evoked potentials
42	2009	11	100% Male	25–34	Inhaled hypoxic gas mixture	20	8	7.6	35–65	Severe	Increased density of EEDS foci in hypothalamus, thalamus, pons, temporal lobe and limbic system
43	2020	40	67.5% Male; 32.5% Female		Hypobaric environment	27	10.6	10.1	75	Moderate	Reduced P3a amplitude of auditory evoked potentials within the first 9 mins of hypoxic exposure. Reduced auditory processing with hypoxia
44	2007	37		25–34	Inhaled hypoxic gas mixture	22.5	8	7.6	62	Severe	Redistribution of EEDS foci. Increased density in hypothalamus, forebrain and limbic system

OTHER EEG ANALYSIS TECHNIQUES

EEG can be a complex, chaotic time series signal. As a result, researchers and clinicians (particularly anaesthetists and intensive care specialists) generally use EEG analysis techniques other than frequency analysis to aid with interpretation.

Evoked potentials and source localisation

Respiratory related evoked potentials provide an insight into the sensory processes underlying respiratory load perception.[45] Electrical equivalents of dipole signals measures the electrical activity of subcortical regions.[42] Studies that utilised respiratory related evoked potentials or electrical equivalents of dipole signals demonstrated stable regulation of cardiovascular and respiratory parameters despite an oxygen deficit.[37,42,44] This was supported by another study which demonstrated no change in either respiratory rate or heart rate with prolonged duration or worsening hypoxic severity.[49] Edlinger, et al. also demonstrated splay between EEG frequency changes and autonomic vital signs with worsening hypoxia.[12] Overall, these studies indicate that autonomic responses can be impaired secondary to cerebral hypoxia. This therefore suggests that solely monitoring autonomic vital signs may not be a useful technique for monitoring cerebral hypoxia and could lead to an inaccurate interpretation of the severity of an individual's hypoxic state.

Quantitative analysis techniques

Bispectral index (BIS™) is a proprietary signal-processed EEG index that produces a single dimensionless number quantifying the shift to predominance of low frequencies – and hence to provide an indication of depth of anaesthesia.[46] The only study reporting the effect of hypoxia on BIS™ readings in adults showed no change across a range of peripheral oxygen saturations from normal to 69%.[38] Most probably the increase in both delta and beta power, as seen in severe hypoxia, would counterbalance each other – thus causing no consistent change in the BIS™ index.

Approximate entropy is a statistical approach of characterising and classifying EEG signals.[36] Lempel-Ziv complexity measures complexity as defined by Kolmogorov, by testing the randomness of a sequence to assess patterns within a deterministic, non-linear EEG signal.[36,39] One study concluded that there is a progressive increase in both approximate entropy and Lempel-Ziv complexity values with worsening hypoxia,[36] whilst another only demonstrated a significant increase in Lempel-Ziv complexity in subjects who were anxious during the hypoxic exposure.[39] Interestingly Jernajczyk, et al. failed to demonstrate significant changes in EEG frequencies in response to hypoxia, but noticed that changes in cortical electrical activity became more apparent by utilising Lempel-Ziv complexity.[39] This emphasises the difficulties, limitations and potential for inaccurate interpretations that can arise by analysing EEG frequency changes alone, and infers greater potential efficacy of quantitative EEG analysis techniques.

LIMITATIONS

Inevitably, there are some limitations in this review. Firstly, the overall quality of evidence was poor, with the comparability domain scoring lowest. The majority of studies did not control for age or gender, nor specify the type of participants recruited, thus study cohorts were poorly comparable with each other. Secondly, the high quantity of articles that were evaluated during the screening process could have created a degree of selection bias. However, each title, abstract and full-text study was reviewed at least twice by three independent reviewers, reducing the probability of incorrectly excluding a relevant study. Thirdly, participants of studies analysed in this review were young. Since EEG changes with age,[50] the results from this systematic review may not accurately reflect how EEG changes with cerebral hypoxia in an older individual and could therefore not be applicable to an older population (> 60 years). Lastly, only 12 studies specified numerical changes in spectral power of EEG frequencies. Whilst these values largely correlated to the overall trends in EEG frequency changes outlined in other studies, further research is needed to properly validate the extent of these changes for each EEG frequency under varying hypoxic exposures and cognitive loads.

FUTURE IMPLICATIONS

Further research is required to investigate the practical and clinical utility of EEG frequency analysis to monitor cerebral hypoxia. Research is also required to evaluate how various factors, such as cognitive load, could influence EEG frequencies. This could involve directly measuring EEG frequencies in participants whilst they perform cognitive tasks in progressively deteriorating hypoxic environments compared to participants who are not subjected to a cognitive load. This would allow more specific assessment into the progression and pattern of EEG changes that can be expected at different hypoxic thresholds and determine how factors such as severity of hypoxic exposure or cognitive load could influence EEG frequencies.

This systematic review has identified quantitative EEG analysis techniques (BIS™, approximate entropy, Lempel-Ziv complexity), that could provide greater clinical utility for monitoring cerebral hypoxia compared to the assessment of EEG frequencies. These quantitative analysis techniques are advantageous as they are usually less expensive and require less expertise to interpret.[9] Further research is required to comprehensively assess how BIS™, approximate entropy and Lempel-Ziv complexity are affected by cerebral hypoxia

in healthy adults, and whether these modalities are more reliable for continuous EEG monitoring compared to the assessment of EEG frequencies.

Conclusions

There is a relationship between acute cerebral hypoxia and EEG frequency changes. Alpha waves decrease whilst delta and theta waves increase in response to moderate and severe hypoxic exposures, although these changes may be affected by factors such as severity of hypoxic exposure and cognitive load. Current evidence on the relationship between quantitative analysis of EEG and cerebral hypoxia is limited. Future research is required to quantitatively define a hypoxia-EEG response curve and how factors such as cognitive load affects this relationship. The comparative utility of analysing EEG frequencies versus quantitative analysis of the EEG also requires further investigation. As part of a study to determine whether prior hypoxic exposure helps recognition of a subsequent hypoxic event among divers, our group is undertaking a series of hypoxic exposures with EEG monitoring of sufficient quality to allow all relevant analyses. A related aim in our currently funded research program is the development of technologies that improve real-time hypoxia detection and reduce the risk of fatal cerebral hypoxic events occurring in divers.

References

1 Mitchell S, Doolette D. Recreational technical diving part 1: an introduction to technical diving methods and activities. Diving Hyperb Med. 2013;43:86–93. PMID: 23813462. [cited 2023 Jul 27]. Available from: https://dhmjournal.com/images/IndividArticles/43June/Mitchell_dhm.43.3.86-93.pdf.

2 Hochachka PW, Clark CM, Brown WD, Stanley C, Stone CK, Nickles RJ, et al. The brain at high altitude: hypometabolism as a defense against chronic hypoxia? J Cereb Blood Flow Metab. 1994;14:671–9. doi: 10.1038/jcbfm.1994.84. PMID: 8014215.

3 Rodrigo J, Fernández AP, Serrano J, Peinado MA, Martínez A. The role of free radicals in cerebral hypoxia and ischemia. Free Radic Biol Med. 2005;39:26–50. doi: 10.1016/j.freeradbiomed.2005.02.010. PMID: 15925277.

4 Malle C, Quinette P, Laisney M, Bourrilhon C, Boissin J, Desgranges B, et al. Working memory impairment in pilots exposed to acute hypobaric hypoxia. Aviat Space Environ Med. 2013;84:773–9. doi: 10.3357/ASEM.3482.2013. PMID: 23926651.

5 Zhang T, Wang Y, Li G. Effect of intermittent hypoxic training on hypoxia tolerance based on single-channel EEG. Neurosci Lett. 2016;617:39–45. doi: 10.1016/j.neulet.2016.01.063. PMID: 26850573.

6 Zani A, Tumminelli C, Proverbio AM. Electroencephalogram (EEG) alpha power as a marker of visuospatial attention orienting and suppression in normoxia and hypoxia. An exploratory study. Brain Sci. 2020;10:140. doi: 10.3390/brainsci10030140. PMID: 32121650. PMCID: PMC7139314.

7 Aird RB, Gastaut Y. Occipital and posterior electroencephalographic rhythms. Electroencephalogr Clin Neurophysiol. 1959;11:637–56. doi: 10.1016/0013-4694(59)90104-X. PMID: 13792196.

8 Frost JD Jr, Carrie JR, Borda RP, Kellaway P. The effects of dalmane (flurazepam hydrochloride) on human EEG characteristics. Electroencephalogr Clin Neurophysiol. 1973;34:171–5. doi: 10.1016/0013-4694(73)90044-8. PMID: 4119530.

9 Hirsch LJ. Brain monitoring: the next frontier of ICU monitoring. J Clin Neurophysiol. 2004;21:305–6. PMID: 15592004.

10 Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. On website The Ottawa Hospital Research Institute [Online]. [cited 2023 Feb 9]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

11 Chatelier G, Galban P, Gouars M, Guillermin M, Benceny C, Santucci G. [Study of tolerance time to hypoxia in pilot trainees, during the course of their aeromedical training in a pressure-lowering cabin]. Rev Corps Sante Armees Terre Mer Air. 1971;12:515–42. PMID: 4257273. French.

12 Edlinger G, Domej W, Lindner G, Pfurtscheller G, Guger C. Effects of a fast cable car ascent on the autonomic and central nervous system assessed by EEG and ECG analysis. In: Conference Proceedings. 2nd International IEEE EMBS conference on neural engineering, 2005. IEEE. doi: 10.1109/CNE.2005.1419608.

13 Balioz NV, Krivoshchekov SG. [Individual typological features in the EEG of athletes after acute hypoxic treatment]. Fiziol Cheloveka. 2012;38:24–32. PMID: 23101237. Russian.

14 Shi Z, Zhao D, Li C, Qian M. Changes on electroencephalogram under acute hypoxia and relationship between tolerant ability to hypoxia and adaptation ability to high altitudes. Sci Sin B. 1983;26:58–69. PMID: 6867681.

15 Shi Z, Zhao D, Gu Z. The influence of acute and chronic hypoxia on the electroencephalogram of human body. Sci Sin B. 1986;29:1065–76. PMID: 3576175.

16 Shi L, Zhang YM, Tetsuo K, Shi ZY, Fang YQ, Denoble PJ, et al. Simulated high altitude helium-oxygen diving. Aerosp Med Hum Perform. 2017;88:1088–93. doi: 10.3357/AMHP.4912.2017. PMID: 29157337.

17 Bertha H, Lorenzonia E, Manowarda K, Lechner H. [Polygraphic studies during an aviation-medical altitude experiment]. Wien Z Nervenheilkd Grenzgeb. 1964;21:297–323. PMID: 14260445. German.

18 Gazivoda N. [Influence of hypoxia on electroencephalographic curve]. Med Glas. 1971;25:233–7. PMID: 5148033. Croatian.

19 Remond A, Soussen G, Lesevre N. [Effects of the inhalation of a gaseous mixture poor in oxygen (5 p. 100) on the EEG of the normal man]. Rev Neurol (Paris). 1960;102:416–22. PMID: 13740784. French.

20 Rice GM, Snider D, Drollinger S, Greil C, Bogni F, Phillips J, et al. Dry-EEG manifestations of acute and insidious hypoxia during simulated flight. Aerosp Med Hum Perform. 2019;90:92–100. doi: 10.3357/AMHP.5228.2019. PMID: 30670118.

21 Tanaka S. [Influence of high altitude environment on brain function]. The Kitakanto Medical Journal. 1982;32:131–43. doi: 10.2974/kmj1951.32.131.

22 Soroko SI, Kurmashev RA, Dzhunusova GS. Rearrangements of the algorithms of interaction between wave components of EEGs in subjects with different mechanisms of brain self-

regulation during adaptation to high altitudes. Hum Physiol. 2002;28:647–56. doi: 10.1023/A:1021187903396.
23 Luft UC, Noell WK. Manifestations of brief instantaneous anoxia in man. J Appl Physiol. 1956;8:444–54. doi: 10.1152/jappl.1956.8.4.444. PMID: 13286207.
24 Burykh EA. Features of the dynamics of the human EEG spectrum at a constant level of acute hypoxia. Neurosci Behav Physiol. 2020;50:231–8. doi: 10.1007/s11055-019-00891-0.
25 Chen Z, Zhang G, Zhou D, Cheng X, Zhu L, Fan M, et al. [Effects of acute high altitude hypoxia on EEG power in different emotional states]. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2020;36:556–61. doi: 10.12047/j.cjap.5978.2020.117. PMID: 33719257. Chinese.
26 Guger C, Domej W, Lindner G, Edlinger G. Effects of cable car ascent to 2700 meters on mean EEG frequency and event-related desynchronization (ERD). Wien Med Wochenschr. 2005;155:143–8. doi: 10.1007/s10354-005-0161-9. PMID: 15966259.
27 Guger C, Krausert S, Domej W, Edlinger G, Tannheimer M. EEG, ECG and oxygen concentration changes from sea level to a simulated altitude of 4000m and back to sea level. Neurosci Lett. 2008;442:123–7. doi: 10.1016/j.neulet.2008.06.075. PMID: 18619520.
28 Kraaier V, Van Huffelen AC, Wieneke GH. Quantitative EEG changes due to hypobaric hypoxia in normal subjects. Electroencephalogr Clin Neurophysiol. 1988;69:303–12. doi: 10.1016/0013-4694(88)90002-8. PMID: 2450729.
29 Papadelis C, Kourtidou-Papadeli C, Bamidis PD, Maglaveras N, Pappas K. The effect of hypobaric hypoxia on multichannel EEG signal complexity. Clin Neurophysiol. 2007;118:31–52. doi: 10.1016/j.clinph.2006.09.008. PMID: 17088101.
30 Pokorski M, Trojecka A, Marczak M, Wierzbicka A, Jernajczyk W. Cortical activity during hypoxic hyperventilation. J Physiol Pharmacol. 2003;54:29–34. PMID: 15886408.
31 Saletu B, Grunberger J, Anderer P. Proof of antihypoxidotic properties of tenilsetam in man by EEG and psychometric analyses under an experimental hypoxic hypoxidosis. Drug Dev Res. 1987;10:135–55. doi: 10.1002/ddr.430100303.
32 Schaffler K. [Pharmacodynamic bioequivalence of piracetam in hypoxic hypoxia]. Arzneimittelforschung. 1986;36:845–9. PMID: 3730020. German.
33 van der Post J, Noordzij LAW, de Kam ML, Blauw GJ, Cohen AF, van Gerven JMA. Evaluation of tests of central nervous system performance after hypoxemia for a model for cognitive impairment. J Psychopharmacol. 2002;16:337–43. doi: 10.1177/026988110201600408. PMID: 12503833.
34 Sokolov E, Steklova P. [Conditioned reflex to time and its course under hypoxic conditions]. Zh Vyssh Nerv Deiat Im I P Pavlova. 1970;20:1123–30. PMID: 5510106. Russian.
35 Ramadan MZ, Ghaleb AM, Ragab AE. Using electroencephalography (EEG) power responses to investigate the effects of ambient oxygen content, safety shoe type, and lifting frequency on the worker's activities. Biomed Res Int. 2020;2020:7956037. doi: 10.1155/2020/7956037. PMID: 32337279. PMCID: PMC7160726.
36 Ding Q, Li G, Wang B, Hu M, Li J. Complexity and topographic analysis of EEG under normal and simulated high altitude acute hypoxia conditions. In: 2005 International Conference on Neural Networks and Brain. IEEE; 2005. doi: 10.1109/ICNNB.2005.1614922.
37 Eckert DJ, Catcheside PG, McDonald R, Adams AM, Webster KE, Hlavac MC, McEvoy RD. Sustained hypoxia depresses sensory processing of respiratory resistive loads. Am J Respir Crit Care Med. 2005;172:1047–54. doi: 10.1164/rccm.200505-699OC. PMID: 15976376.
38 Ikeda T, Yamada S, Imada T, Matsuda H, Kazama T. Influence of hypobaric hypoxia on bispectral index and spectral entropy in volunteers. Acta Anaesthesiol Scand. 2009;53:891–4. doi: 10.1111/j.1399-6576.2009.01945.x. PMID: 19397504.
39 Jernajczyk W, Sobańska A, Marczak M. The influence of acute progressive hypoxia on bioelectrical activity of the brain. J Physiol Pharmacol. 2006;57:165–74. PMID: 17072043.
40 Kida M, Imai A. Cognitive performance and event-related brain potentials under simulated high altitudes. J Appl Physiol (1985). 1993;74:1735–41. doi: 10.1152/jappl.1993.74.4.1735. PMID: 8514690.
41 Miszczak J, Nowicki J. [Evoked average corticoauditory responses in the course of controlled hypoxia]. Otolaryngol Pol. 1975;29:343–7. PMID: 1161298. Polish.
42 Rozhkov VP, Soroko SI, Trifonov MI, Bekshaev SS, Burykh EA, Sergeeva EG. Cortical-subcortical interactions and the regulation of the functional state of the brain in acute hypoxia in humans. Neurosci Behav Physiol. 2009;39:417–28. doi: 10.1007/s11055-009-9160-4. PMID: 19430971.
43 Seech TR, Funke ME, Sharp RF, Light GA, Blacker KJ. Impaired sensory processing during low-oxygen exposure: a noninvasive approach to detecting changes in cognitive states. Front Psychiatry. 2020;11:12. doi: 10.3389/fpsyt.2020.00012. PMID: 32082202. PMCID: PMC7006237.
44 Soroko SI, Bekashaev SS, Rozhkov VP. EEG markers of the disturbed systemic brain activity in hypoxia. Hum Physiol. 2007;33:546–58. doi: 10.1134/S0362119707050052.
45 Webster KE, Colrain IM. The relationship between respiratory-related evoked potentials and the perception of inspiratory resistive loads. Psychophysiology. 2000;37:831–41. doi: 10.1111/1469-8986.3760831. PMID: 11117463.
46 Myles P. Bispectral index monitoring in ischemic-hypoxic brain injury. J Extra Corpor Technol. 2009;41:P15–9. PMID: 19361035. PMCID: PMC4680226.
47 Li Y, Lou B, Gao X, Sajda P. Post-stimulus endogenous and exogenous oscillations are differentially modulated by task difficulty. Front Hum Neurosci. 2013;7:9. doi: 10.3389/fnhum.2013.00009. PMID: 23386819. PMCID: PMC3560344.
48 Xi C, Sun S, Pan C, Ji F, Cui X, Li T. Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: wakefulness, moderate sedation, deep sedation and recovery. PLoS One. 2018;13:e0199120. doi: 10.1371/journal.pone.0199120. PMID: 29920532. PMCID: PMC6007908.
49 Foster GE, McKenzie DC, Milsom WK, Sheel AW. Effects of two protocols of intermittent hypoxia on human ventilatory, cardiovascular and cerebral responses to hypoxia. J Physiol. 2005;567:689–99. doi: 10.1113/jphysiol.2005.091462. PMID: 15975977. PMCID: PMC1474187.
50 Vysata O, Kukal J, Prochazka A, Pazdera L, Simko J, Valis M. Age-related changes in EEG coherence. Neurol Neurochir Pol. 2014;48:35–8. doi: 10.1016/j.pjnns.2013.09.001. PMID: 24636768.

Acknowledgements

The authors would like to thank Anne Wilson (University of Auckland librarian) for her guidance and support with creating the MEDLINE search string.

Funding

This work was supported by funding from the Office of Naval Research Global (ONRG), United States Navy (N62909-22-1-2003) and ANZCA Foundation; Australian and New Zealand College of Anaesthetists (AEG22/002).

Conflicts of interest

Simon J Mitchell is the Editor of Diving and Hyperbaric Medicine. He took no part in the peer-review and decision-making processes for this paper, which was managed entirely by the Deputy Editor, Dr Lesley Blogg. There were no other conflicts of interest.

Submitted: 4 June 2023
Accepted after revision: 27 July 2023