

Intermittent Oxygen Fasting & Digital Technologies: From Antistress & Hormones Regulation to Wellbeing, Bliss & Higher Mental States

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Abstract. Low oxygen breathing has been the subject of considerable research in recent years. The present review aims to determine the physiological and neuropsychological benefits of low-oxygen training. Specifically, we explored the ways low oxygen affects hormones, neurotransmitters and growth factors responsible for neuroplasticity, higher cognition and positive emotions. In addition, we shed light on the importance of hypoxia to expand the conscious experience. Furthermore, we investigate the role of digital technologies in assisting hypoxic training. The results showed that, when hypoxia occurs, the human body puts into action the amazing survival mission which reveals unexplored alternative plans and healing pathways. Oxygen deprivation, under certain circumstances, has beneficial effects on cognition, mood and consciousness. It was observed an increase in growth factors, which are responsible for tissue repair and regeneration. Hypoxia also was found to stimulate the hormones of pleasure, happiness, pain tolerance, socialization and relaxation. Interestingly, people under hypoxic conditions are more likely to have transcendental experiences -even to develop 'superhuman' abilities. Digital technologies facilitate the safe implementation of hypoxic training enabling users to take control of a powerful tool, which is none other than breathing. Metacognition in breathing can help people consciously and safely manipulate their breathing by moving themselves away from their comfort zone and exploring new pathways to rewire their brains and plumb the depths of their physical, cognitive, emotional and spiritual potential. Our findings suggest that hypoxic training could be an effective intervention strategy with important therapeutic benefits for people with learning and other disabilities (i.e. adhd, memory deficits, autism, motor, impairments, depression, generalized anxiety disorder). Future educators, therapists and families should be trained to appropriately apply simple hypoxic training exercises even in the educational context. For that reason, research into the physiological and neuropsychological mechanism that is affected by hypoxic training for individuals with learning or other disabilities is necessary.

Keywords. Oxygen deficit, hypoxia therapy, antistress markers, cognitive improvement, mood stabilization, special education, altered states of consciousness, growth factors, beneficial hormonal responses, metacognition, brain rewiring, metacognition in breathing, low hypoxic doses, hypoxic breathing exercises, voluntary trance, superhuman abilities

1. Introduction

The term hypoxia is closely related to the organ, tissue, and even cell type. A hypoxic state signifies that an imbalance of oxygen is present and normal function is compromised as a result of this imbalance. The imbalance of oxygen could result from a lack of oxygen or an excessive oxygen demand. Normal function in this context includes carrying out essential bodily or

cellular functions such as heart muscle beating or a neuron firing an action potential, also known as homeostasis. Hypoxia can be intermittent, acute, or chronic. Hypoxic conditions begin with a prolonged lack of oxygen. Hypoxia could be simply defined as a condition during which tissue fails to receive this amount of oxygen. When oxygen is not delivered in sufficient quantities, the body undergoes immediate responses (Choudhury, 2018). During this period, the human body puts into action the amazing survival mission which has many alternative plans and healing pathways.

Intermittent hypoxia is defined as repeated episodes of hypoxia with intervening periods of normoxia. These cycles are repeated at various intervals (Malshe, 2011). Intermittent hypoxia has generally been perceived as a high-risk stimulus because it is thought to initiate detrimental cardiovascular, respiratory, cognitive, and metabolic outcomes (Mateika et al., 2015). However, the beneficial role of hypoxia has received less attention, perhaps because it is not well-understood that outcome measures following exposure to hypoxia may be linked to the administered dose (Mateika et al., 2015).

Hypoxic training or conditioning dates back from the traditional medical remedy used in ancient times. For example, in the Carpathian Mountain region, children who suffered from asthmatic bronchitis ranged on foot for 7 days on a high mountain (Serebrovskaya, T. V., & Xi, L. (2015). In India, yogic treatment for various diseases includes low oxygen breathing exercises. Many researchers use hypoxia as a training tool simulating the conditions of high altitudes to train the pilots of small aircraft and mountaineers. In addition, low oxygen training is used as a training method to improve the performance of top athletes (Malshe, 2011; Shaw et al., 2021)

According to Navarrete & Mitchell (2014), several parameters determine whether hypoxia will cause beneficial or detrimental effects: (a) the severity of hypoxia (e.g. the level of hypoxemia), (b) the duration of hypoxia, (c) the number of hypoxia episodes per day, (d) the pattern of presentation (e.g. multiple episodes per day), (d) the cumulative duration of exposure (minutes, hours, days), (e) regulation of other variables such as the level of arterial carbon dioxide.

Smartphones and breathing applications offer novel opportunities to facilitate breathing practice (Drigas & Mitsea, 2022). Breathing training apps are always available to assist users everywhere and whenever they need them. Moreover, the price of a smartphone app is usually reasonable, and it is quite easy to find free apps. In general, smartphones are increasingly seen as a powerful m-health instrument for treatment and training and some authors predict that the mobile phone will emerge as the preferred personal coach for the 21st century. However, Mobile apps for breathing training lack formal evaluation in the literature (Chittaro & Sioni, 2014; Morris & Guilak, 2009). Another novel approach that has been explored for the delivery of health interventions except for mobile health (mHealth) is mHealth gaming. The “gamification” of mHealth apps engaging badges, leaderboards, points, levels, and challenges seem extremely promising. In addition, most applications use musical elements, which relax, motivate, and facilitate the breathing experience (Pham et al., 2016).

Virtual reality is already recognized as an effective tool for breathing training (Mitsea, Drigas & Skianis, 2022). Virtual reality combined with biofeedback identifies physiological signals by sensors and provides feedback to the user in real-time. Biofeedback protocols aim to develop the user’s ability to consciously control their respiration (Giggins, Persson & Caulfield, 2013; Rockstroh et al., 2021). Respiratory biofeedback also aims to increase the awareness of the breath, help the trainees to better monitor their current breathing style, regulate and adapt it if necessary and offer reinforcement learning by providing pleasing and rewarding feedback stimuli (Gaume et al., 2016). VR also employs virtual avatars as training aids, changing users’

perspective, or evoking a feeling of embodiment described as body ownership illusion (Czub and Kowal, 2019). In current studies, virtual reality breathing-based biofeedback training offers engaging game-like action contexts. Games offer the possibility to re-create a genuine feeling of threat and immersion, moderate enough for learning to take place while at the same time boosting engagement (Michela et al., 2021).

Nonetheless, the scientific evidence for the beneficial effects of intermittent hypoxic training/therapy on physiological and neuropsychological operations remains obscure despite the numerous investigations over the past decades.

2. Method

The purpose of the current review study is to shed light on the benefits of hypoxia in physiological and neuropsychological mechanisms. Moreover, we investigate the role of digital technologies in hypoxic training. We systematically searched clinical and technical databases including Scholar Google, Pubmed, IEEE Xplore, Scopus, Science Direct following a comprehensive search strategy with main research terms the following: hypoxic training, intermitted hypoxia, hypoxic altitude training, human growth factors, hormonal responses, neurotransmitters, low oxygen breathing techniques, blood flow restriction. Priority was given to experimental research studies. Regarding research limitations, we can mention the lack of experimental studies evaluating exclusively hypoxic training via digital technologies. In addition, there was a limited number of large-scale studies to determine the beneficial effects of hypoxic training.

3. Results

Hypoxia & neurohormonal/neurotransmitters benefits

Neurotransmitters and modulators are important regulators of the physiological system. The synthesis of several neurotransmitters/ modulators is regulated by O₂-requiring rate-limiting enzymes. Consequently, hypoxia resulting from perturbations in O₂ homeostasis can alter neurotransmitter synthesis either positively or negatively (Kuman, 2011). In the following section, we will focus on the beneficial outcomes of low oxygen on hormonal responses and neurotransmitters synthesis and release.

Catecholamines

Catecholamines comprising dopamine, norepinephrine and epinephrine are expressed in many brain regions of the brain, adrenal medulla, and play a significant role in fundamental physiological processes and neuropsychological processes (Kumar, 2011). Catecholamines influence the autonomic nervous system and alter mood as well as cognitive and metacognitive abilities (Drigas & Mitsea, 2021).

Noradrenaline & Adrenaline: The hormones of alertness

Rostrup (1998) studied plasma catecholamines after stepwise ascent to a high altitude (4.200m). Two days after arrival, it was revealed a temporary reduction in plasma catecholamines. After a week there was a steady increase towards normal levels. This study showed that **noradrenaline** and **adrenaline** are positively related to arterial oxygen saturation. The researcher concluded that short-term hypoxia does not increase catecholamines, rather plasma levels decreased.

Cortisol: The stress hormone

Yan et al. (2016) aimed to measure the effects of different levels of hypoxia on hormonal responses on 5 weeks of resistance training. Twenty-five male subjects were randomly assigned

into 3 experimental groups that performed 10 sessions (2 sessions per week) of barbell back squat (10 repetitions, 5 sets, 70% 1 repetition maximum [RM]) under normoxia (NR, $F_iO_2 = 21\%$) and hypoxia (HL, $F_iO_2 = 16\%$; HH, $F_iO_2 = 12.6\%$). **Cortisol** concentration was significantly lower in the hypoxia group than the value in the normoxia group in the last training session.

Dopamine: the hormone of pleasure

Gamboa et al. (2006) evaluated the chronic effects of hypoxia on plasma catechols and blood volume, by studying these parameters during hypoxia at high altitude and shortly after exposure to normoxia at sea level. Participants were 20 male, native high-altitude residents of Cerro de Pasco, Peru (4338 m). It was found that all subjects had higher plasma norepinephrine, dopamine, and dihydroxyphenylglycol levels in hypoxia conditions.

Orset et al. (2005) determined the *in vivo* mechanisms underlying the striatal dopamine efflux induced by mild hypoxaemic hypoxia. For that purpose, the extracellular concentrations of dopamine and its metabolite 3,4-dihydroxyphenyl acetic acid were simultaneously measured using brain microdialysis during acute hypoxic exposure (10% O_2 , 1h) in awake rats. The results showed that hypoxia resulted in a +80% increase in brain dopamine levels.

Ray et al. (2011) investigated how hypoxia modulates brain biogenic amines. Thirty adult rats were exposed to simulated altitude ~ 7620 m, 282 mm Hg, partial pressure of O_2 59 mm Hg for 7 and 14 days continuously in an animal decompression chamber. After 7 and 14 days of hypoxia, brain norepinephrine and dopamine levels were significantly increased in the frontal cortex, brain stem, cerebellum, pons and medulla.

Melatonin: the hormone of sleep

Calderon, Moraga & Moraga (2022) aimed to assess the relationship between hypoxia, sleep quality and plasma melatonin concentrations in 288 workers exposed to chronic intermittent hypobaric hypoxia. The participants were recruited from five altitudes. The data confirmed that hypoxia elevated morning melatonin levels. The researchers also found that lower arterial oxygen saturation correlates with higher values of melatonin, especially at 4500 m.

Kaur et al. (2002) examined the effects of hypoxia exposure on melatonin. Rats were exposed to an altitude of 8000m for 2hr in an altitude chamber. Blood samples were collected at various time intervals and the pineal glands were processed for electron microscopy and immunohistochemistry. The plasma melatonin showed a steady increase peaking at 7 days.

De Aquino Lemos et al. (2018) evaluated the effects of moderate physical exercise performed under hypoxic conditions on melatonin and sleep. Forty healthy men were randomized into four groups: (a) normoxia, (b) hypoxia, (c) exercise under normoxia and (d) exercise under hypoxia. Venous blood samples for the melatonin measurement were obtained on the first & second day at 7:30 am as well as on the first and second nights at 10:30. On the second night, melatonin was higher in the hypoxic group than in the normoxic group. However, both were lower than the values of the exercise under the hypoxia group. The results indicate that hypoxia under certain circumstances can increase melatonin levels.

γ -Amino Butyric Acid (GABA): The hormone of relaxation

Wood, Watson & Ducker (1968) exposed animals to hypoxic environments either by supplying them with breathing mixtures low in oxygen or by exposing them in a decompression chamber to simulated altitude. Both methods of producing hypoxia brought about significant increases in brain GABA levels. Elevated GABA levels reached maximal concentration 60 min after the initiation of breathing the hypoxic mixtures. Extension of the exposure brought about a gradual decline in GABA level from the maximal value reached.

Oxytocin: the hormone of love & socialization

Chen et al. (1999) investigated the impact of hypoxia on the release of oxytocin in adult male rats. Hypoxia was achieved in a hypobaric chamber. The results showed that acute hypoxic stress increased the release of oxytocin. However, chronic hypoxia (5–25 days) had no statistically significant influence on oxytocin levels. The results also suggested that hypoxia produced an intensity and duration-dependent release of oxytocin and that such release might be modulated in part by hypoxia-activated high circulating glucocorticoids and their negative feedback on the release of corticotropin-releasing hormone (CRH).

Hypoxia increases endogenous opioids

Anandamide: the cannabinoid neurotransmitter of bliss

Anandamide is an endogenous cannabinoid neurotransmitter. Feurecker et al. (2012) investigated the effects of exercise at different altitudes on the endocannabinoid system in 12 trained healthy volunteers. Three protocols were analyzed: (a) physical exercise at a lower altitude (2,100 m.), (b) physical exercise by active ascent to a high altitude (3,196 m.), and (c) a helicopter ascent to 3,196 m. The results showed that blood anandamide concentrations were significantly enhanced when exercise was combined with moderate hypoxic conditions at high altitude.

Enkephalin: The painkiller

Chen & Du (2000) investigated hypoxia effects on leucine-enkephalin (L-ENK) levels of the median eminence of the hypothalamus in rats. Hypoxia was stimulated in a hypobaric chamber. Acute hypoxia (10.8% O₂) enhanced L-ENK levels.

Beta-Endorphins: The happiness hormones

According to various studies, hypoxia stimulates the release of beta-endorphins. For instance, hypoxemia in infants due to birth asphyxia or other conditions acts as a strong stimulus for plasma beta-ED release (Sankaran, 1984; Ruth et al., 1986).

Serotonin: The mood stabilizer

Ling et al. (2001) evaluated the hypothesis that chronic intermittent hypoxia elicits plasticity in the central neural control of breathing via serotonin-dependent effects on the integration of carotid chemoafferent inputs. Adult rats were exposed to 1 week of nocturnal hypoxia (11–12% O₂/air at 5 min intervals; 12 hr/night). The results suggested that hypoxia elicits unique forms of serotonin-dependent plasticity in the central neural control of breathing.

Hypoxia reduces hunger hormones

Shukla et al. (2005) found that *hypoxic breathing training* results in the regulation of hormones that are responsible for appetite regulation and energy balance namely, **leptin** and **ghrelin**. Specifically, it was found that hypoxia reduced the hunger hormone (ghrelin) while it increased the leptin which is responsible to inhibit hunger.

Hypoxia improves brain blood flow

Liu et al. (2017) examined cerebrovascular responses to intermittent hypoxia in eight healthy men breathing 10% O₂ for 5 cycles, each 6 min, interspersed with 4 minutes of room air-breathing. The results showed that hypoxia increased brain blood flow by 20%. Although blood oxygen saturation dropped under the therapeutic range (67%), the subjects did not report discomfort or stress. Thus, this study revealed that brief exposures to cyclic intermittent hypoxia can increase brain blood flow and as a result cognitive abilities such as attention. The authors suggested that the same effect can be easily achieved using breath holds.

Hypoxia promotes Neurogenesis & Synaptic plasticity markers

An oxygen deficiency in the brain is a medical emergency that can irreversibly harm nerve cells. Nonetheless, there is growing evidence that hypoxia can be an essential signal for growth to some extent (Butt et al., 2021).

Increasing evidence demonstrates that the stimulation of hippocampal neurogenesis leads to anti-depressant effects. Zhu et al. (2010) explored the potential regulatory capacity of an intermittent hypobaric hypoxia regimen on hippocampal neurogenesis and its possible antidepressant-like effect. It was found that intermittent hypoxia promoted the proliferation of endogenous neuro-progenitor leading to more newborn neurons in the hippocampus in adult rats. Interestingly, hypoxia produced antidepressant-like effects in multiple animal models screening for antidepressant activity. Furthermore, hypoxia stably increased the expression of BDNF in the hippocampus; both the antidepressant-like effect and the enhancement of cell proliferation induced by intermittent hypoxia.

According to Butt et al. (2021) oxygen deficit, promotes nerve cell growth. They showed that physiological (endogenous) hypoxia is likely a respective lead mechanism, regulating hippocampal plasticity via adaptive gene expression. They also reported that complex motor-cognitive challenges can also cause mild hypoxia across essentially all brain areas, with hypoxic neurons particularly abundant in the hippocampus. An oxygen shortage may be one reason that induces comprehensive brain activation and thereby improve global brain function including mood and emotional well-being in healthy subjects and patients. Mild hypoxia activates, among other markers, the growth factor erythropoietin (EPO), which, in turn, stimulates red blood cells and activates the formation of new synapses and nerve cells. This mechanism could explain why physical and mental exercises boost mental performance.

Hypoxia boosts Growth factors

Yan et al. (2016) investigated how hypoxia influences growth factors during resistance training. Twenty-five male subjects performed barbell back squats either under normoxia or hypoxia. Concentrations were measured before (Pre) and at 0, 15 & 30 minutes after exercise in the first and last training sessions. In the first session, the growth hormones were higher for the hypoxic group. In the last session growth hormones of the hypoxic group were still significantly higher than the normoxia group. This study showed that resistance exercise in hypoxia led to a greater elevation of growth hormones.

Malshe (2011) suggests multiple health positive effects of intermittent hypoxia, such as an elevation in hemoglobin by elevating erythropoietin, an increase in vascular endothelial growth factor (VEGF) contributing to the creation of coronary collaterals, a decrease in blood pressure and lessened effects of aging by resistance to cellular degradation.

Hypoxia regulates Glucose metabolism

De Groote et al. (2018) examined whether hypoxic training improves glucose metabolism and insulin sensitivity. Fourteen adolescents with obesity were assigned to six weeks of exercise training either in normoxic or hypoxic conditions (FiO₂ 15%). Before and after the training, oral glucose tolerance tests, blood, and morphological analyses, and physical performance tests were performed. It was revealed, that, after training, hypoxia not normoxia improved glucose tolerance and decreased insulin levels. According to the researchers, exercise training in hypoxia could be an interesting strategy against insulin resistance and type 2 diabetes development in people with obesity.

Hypoxia reduces oxidative stress and enhances antioxidant markers

Ohkuwa et al. (2004) explored the effects of hypoxia training on pivotal antioxidant markers and markers of oxidative stress, such as glutathione levels and 8-OHdG respectively. Rats were divided into three groups: a hypoxia and exercise group, hypoxia and sedentary group, and a normoxia and sedentary group. It was found that moderate hypoxia especially combined with exercise can reduce oxidative stress markers and increase antioxidant markers.

Hypoxia induces the enzyme Nitric Oxide Synthase (NOS). Nitric oxide has been assigned different roles in different tissues. Widely, it is one of the defense mechanisms against oxidative

damage. Thus, more nitric oxide can protect the tissues better. In addition, induces p53 “Guardian of the genome”, which is a transcription regulation factor and it has a protective role in DNA damage. These techniques also help stem cells to survive (Malshe, 2011).

Hypoxia reduces inflammatory markers

Shi et al. (2014) conducted a crossover study on healthy subjects to identify the effect of hypoxic training on inflammatory and metabolic risk factors. Fourteen healthy participants performed treadmill exercise 3 days per week for 4 weeks under either normobaric hypoxic or normobaric normoxic conditions for 50 min (including a 5-min warm-up and 5-min cool down) after a 30-min rest period. The results showed that C-reactive protein, a marker that indicates general levels of inflammation in the body was significantly lower. The authors concluded that regular short-term hypoxic training may more effectively reduce inflammation compared to training performed under normoxic conditions.

Hypoxia boosts brain oscillations for neurorehabilitation (δ -, θ -, and α -Band Power)

Papadelis et al. (2007) evaluated the effect of hypobaric hypoxia on multichannel EEG signal complexity. Multichannel EEG, pO₂, pCO₂, ECG, and respiration measurements were recorded from 10 subjects exposed to three experimental conditions (100% oxygen, hypoxia, recovery) at three-levels of reduced barometric pressure. The results showed a significant increase in the total power of theta and alpha bands during hypoxia.

Komori (2018) investigated the effects of a breathing method known as Okinaga on brain waves and autonomic nervous system function. According to this breathing technique, individuals perform extreme prolongation of expiration breathing. The results showed that theta and alpha 2 waves (9-11 Hz) increased, and beta waves decreased. Therefore, parasympathetic dominance was observed as Okinaga progressed. These findings suggest that deep breathing increases the brain waves of relaxation and resilience.

Ozaki et al. (1995) investigated the multichannel human EEG signals in subjects exposed to high altitude conditions. The spectral power of the theta frequency band in anterior brain areas increased significantly in the 5000 m and 6000 m conditions.

Hypoxia relieves anxiety & improves mood states

de Aquino-Lemos et al. (2016) evaluated the effect of two sessions of acute physical exercise at 50% VO_{2peak} performed under hypoxia (equivalent to an altitude of 4500 m for 28 h) on sleep, mood and reaction time. Forty healthy men were randomized into 4 groups: Normoxia (NG) (n = 10); Hypoxia (HG) (n = 10); Exercise under Normoxia (ENG) (n = 10), and Exercise under Hypoxia (EHG) (n = 10). Tension, anger, depressed mood, vigor and reaction time scores improved after exercise under hypoxia. The authors concluded that acute physical exercise at 50% VO_{2peak} under hypoxia improves sleep efficiency, improves mood and reaction time.

Meng, Wang & Li (2020) investigated the effects of intermittent hypoxia on anxiety-like behaviors. Exposure to hypoxia significantly increased cognitive performance and decreased anxiety-related behaviors in mice. Interestingly, the intervention revealed the neuroprotective effect of hypoxia exposure on hippocampal neurogenesis. Intermittent hypoxia significantly lowered amyloid beta levels in the hippocampus, which are responsible for memory impairments.

Kushwah et al. (2016) explored the neuroprotective role of intermittent hypobaric hypoxia in unpredictable chronic mild stress induced depression-like behavior in rats. The findings of this study demonstrated that intermittent hypoxia has a therapeutic potential similar to an antidepressant in animal model of depression and could be developed as a preventive therapeutic option against this pathophysiological state.

Hypoxia improves executive functions & cognitive performance

Wang et al. (2020) examined whether intermittent hypoxic training can improve mild cognitive impairment in elderly patients. Seven participants alternately breathed 10% O₂ and room-air, every 5 minutes, for 8 cycles/session, 3 sessions/wk for 8 weeks. The patients' resting arterial pressures fell and cerebral tissue oxygenation increased following hypoxia. Intermittent hypoxia training enhanced hypoxemia-induced cerebral vasodilation and improved mini-mental state examination and digit span scores. The researchers concluded that adaptation to moderate hypoxia may enhance cerebral oxygenation and hypoxia-induced cerebrovasodilation while improving short-term memory and attention.

Huber et al. (2018) evaluated data collected from a total of 91,642 interviews and 73,123 children with the aim to support the hypothesis that mean state altitude is a significant predictor of ADHD prevalence. Analysis of two large CDC datasets indicated that ADHD prevalence decreases with mean state altitude. The symptoms of ADHD may be ameliorated by increases in brain dopamine that are known to be associated with hypobaric hypoxia. These observations may have treatment implications for providers and shed light on using natural environmental interventions for ADHD.

Loprinzi et al. (2019) evaluated the effects of acute hypoxia exposure on memory interference, the phenomenon in which some memories interfere with the retrieval of other memories making it difficult to recall similar material. Twenty-one participants completed two laboratory visits, involving 30 min of exposure to either hypoxia or normoxia. The results demonstrated that acute hypoxia exposure was facilitative in reducing memory interference.

According to Coreira et al. (2021) intermittent hypoxic conditioning is a powerful non-pharmacological procedure to enhance brain resilience. The researchers investigated the potential long-term protective impact of hypoxia against Alzheimer-related phenotype, putting a special focus on cognition and mitochondrial bioenergetics and dynamics. Interestingly, hypoxia was able to prevent anxiety-like behavior and memory and learning deficits and significantly reduced brain cortical levels of amyloid- β . The intervention also caused a significant increase in brain cortical levels of glucose and a robust improvement of the mitochondrial bioenergetic profile. It was also observed a significant increase in both glutamate and GABA levels in the brain cortex.

Komiyama et al. (2017) examined the combined effects of acute exercise and severe hypoxia on cognitive function. The participants completed cognitive tasks at rest and during moderate exercise under either normoxic or severe hypoxic conditions. The results showed that cognitive performance improved during exercise under hypoxia, without sacrificing accuracy.

Serebrovska et al. (2019) examined the effects of intermittent hypoxic-hyperoxic training on elderly patients with mild cognitive impairment. Twenty-one participants (age 51–74 years) took part in this study. Each session consisted of four cycles of 5-min hypoxia (12% F_IO₂) and 3-min hyperoxia (33% F_IO₂). It was found that hypoxia improves cognitive function and decreased circulating biomarkers of Alzheimer's disease in patients with Mild Cognitive Impairment.

Hypoxia & Altered States of Consciousness: From normal states of consciousness to higher states and spiritual experiences

Hypoxia can have a major impact on consciousness. Hypoxic breathing can lead people to experience altered states of consciousness, even loss of consciousness (Bickler et al., 2017). After exposure to low oxygen environments, there is a period of useful consciousness. During this period, subjects can effectively and safely perform tasks that require mental clarity. However, systematic training is required to recognize when hypoxia starts to have detrimental effects (Shaw et al., 2021). The intentional acute starvation of oxygen through hypoxia can shift

consciousness to a euphoric state leading to heightened excitement or transcendental experiences (Chater, 2021; Zaviačič, 1994).

Yogi, Samadhi, Fakir, ascetic monks, and expert meditators possess otherworldly abilities. They can enter a trance state, a quiescent state in which they can withstand extreme pain with complete composure. Other Yogies can be buried alive and after digging them up to restore their consciousness. To voluntarily achieve the state of trance, they use respiration as a tool to minimize oxygen intake. Yogis can control their respiration as well as heart rate to require a fraction of the number of breaths and volume of oxygen compared with normal individuals (Manno, 2019). For instance, some trained people can take one breath per minute for one hour (Miyamura et al., 2002).

The fundamental revelations to the founders of well-known religions, among many other spiritual experiences, had occurred on a mountain. These revelation experiences share many phenomenological components like feeling and hearing a presence, seeing a figure or lights. In addition, similar experiences have been reported by non-mystic contemporary mountaineers. The similarities between these revelations on mountains and their appearance in contemporary mountaineers suggest that exposure to hypoxia might affect functional and neural mechanisms, thus facilitating the experience of a revelation. Acute and chronic hypoxia significantly affect the temporo-parietal junction and the prefrontal cortex and both areas have also been linked to altered own body perceptions and mystical experiences (Arzy et al., 2005).

Bao et al. (2019) conducted a single-blind, randomized controlled trial to explore the effect of intermittent hypoxia training on 52 patients with dizziness. Normobaric hypoxia condition was applied by exposing subjects to 5 cycles of 10% O₂ for 5 min followed by room air for 5 min. Subjects inspired hypoxic air through an air-cushioned disposable face-mask or room air directed by a 3-way valve. All subjects practice intermittent hypoxia 50 minutes per session, 5 times per week for 4 weeks. The main new finding of this study was that intermittent hypoxia training significantly improved dizziness symptoms and reduced the frequency of dizziness.

Methods for achieving hypoxia

-Breath control Training with low-oxygen breathing exercises

Restricting the frequency of breathing to recreate a hypoxic effect is considered a successful training method. Controlled frequency breathing is a common training modality involving holding one's breath for approximately 7-10 strokes before taking another breath (Burtch et al., 2017). Breath-hold exercises (i.e. Kumbhaka pranayama) constitute a traditional way to induce hypoxia. Taking a breath, holding it for a prescribed time then repeating the process (Malshe, 2011). Breathing techniques that require prolonged expiration or cooling breathing techniques can be used as methods of hypoxic training (Koromi, 2018; Thanalakshmi et al., 2014).

-Localized hypoxia via blood flow restriction: The blood flow restriction (BFR) technique involves the application of a tourniquet, inflatable cuff or elastic knee wraps around the proximal end of a limb to occlude distal blood flow, thus inducing a localized hypoxic environment during exercise. BFR is also combined with exercises such as resistance exercises. Indeed, research reveals that these techniques are significantly associated with growth factor elevations, augmented positive hormonal responses, and pain management (Scott et al., 2014).

-Chanting: Chanting is a form of rhythmic, repetitive vocalization practiced in a wide range of cultures. In many traditions, chanting leads to oxygen deprivation inducing mystical states, an altered state of consciousness characterized by a profound sense of peace (Perry, Polito & Thompson, 2021).

-Inhaling hypoxic gas mixtures via face masks or larger chambers (Serebrovskaya & Xi, 2016).

- **Rebreathing (paper bag):** Treatment using the paper bag and rebreathing method can help the patients with anxiety or panic to reduce oxygen levels bringing a state of resilience (Kobayashi et al., 2014).

The Role of Digital Technologies in Low-Oxygen Training

Digital technologies and ICTs [79-84] have made a breakthrough in various domains of education, via mobiles [75-78] reached larger communities, and also have been used for training and development of metacognitive skills, emotional intelligence and executive functions [85-95].

More specifically digital technologies are used for hypoxia monitoring and training as follows.

Pulse oximetry (pulse ox) is an expedient and accurate tool to non-invasively measure the oxygenation status of any patient. Wearable technology and devices such as blood oxygen iPhone apps can be effective tools for tracking blood oxygen and getting alerts about oxygen levels. By using this technology individuals can be capable of obtaining reliable and valid measurements helping them to monitor and consciously control their breathing patterns. Thus, these applications can facilitate individuals' hypoxic training (Jordan et al., 2020).

Breathing apps among the Health & Fitness category of mobile applications, there are available *Hypoxic* -Breathing Exercises apps (<https://apkaio.com/app/com.lanius.kenoma.pob>). Breathing exercises with the *Hypoxic app* help subjects to improve adaptability and performance, reduce stress and anxiety, improve mood and concentration and lower blood pressure. It records and analyses HRV (Heart Rate Variability) during exercise sessions. It employs pranayama breathing techniques such as Vishama-vritti, Sama-vritti, Antara kumbhaka, Bahir kumbhaka.

Appnea is a freely available app that helps you track how long you hold your breath, without interrupting your breathing exercise (Villanueva et al., 2017; Isetta et al., 2015).

Chittaro and Sioni (2014) evaluated three different designs for breathing training apps. The first employed audio instructions, while the other two included visualizations of the breathing process. Applications that use visualization may display a circle (or a sphere) that expands and contracts equally with the expansion and contraction of the human lungs during the breathing activity. The results showed that breathing training apps can effectively improve the breathing process. Most important, the researchers found that applications that utilize visualization produce better results both objectively (measured deepness of breath) and subjectively (users' preferences and perceived effectiveness). Thus, breathing training apps could help users to overcome hyperventilation and the effects of fast and shallow breathing that may result in symptoms of intense anxiety and panic.

Bruggeman and Wurster, S. W. (2018) presented a virtual reality stress reduction mobile application that acts as a teaching tool for breathing training by utilizing real-time biofeedback. It is designed to attain and maintain the user's attention towards the breathing practice. The virtual experience begins by having the user strap a pressure sensor around their waist. This sensor is connected to an Arduino board and breadboard that transmit the data received from the pressure sensor to the mobile application via Bluetooth. This information is then processed into the digital application and provides biofeedback in the virtual environment. The user places the phone inside their mobile headset of choice and runs the application. This brings the user into the virtual healing space where he/she can get comfortable and begin.

Benton, Courtney & Warren (2019) investigated whether telehealth hypoxic breath training could alleviate sleep disturbed breathing. Seven participants took part in this study. Subjects performed prompted breathing sequences, combining six mildly hypoxic breath-holds with

relaxed controlled breathing, 20 minutes daily over 6 weeks. Wireless finger-tip PPG/SpO₂ sensors monitored sessions. Data were analyzed for heart and breathing rates, HRV, SpO₂, vagal tone and breath-holding times (BHT). The results showed that daily training using mild self-imposed hypoxia with intervening hypopneic intervals via telehealth showed significant reductions in snoring especially at high intensities indicating improved upper airway responsiveness.

The rapid advance of intermittent hypoxic therapy has led to the development of different medical equipment – hypoxicators – for its implementation in sports practice, military operations and also for clinical application (Lopata & Serebrovskaya, 2012).

Airofit PRO is a smart breathing training device. The AirOFit PRO™ is a small, portable, lightweight, noninvasive, mouth-pressure manometer with a rubber-flanged mouthpiece for assessment and training the respiratory muscles. AirOFit PRO™ contains pressure sensors and a Bluetooth transmitter. This allows to measure the breathing patterns and visualize them on the phone via the AirOFit PRO™ Sport mobile app (Stavrou et al., 2021).

Under certain conditions, hypoxic breathing can be beneficial for health and performance. These "uncomfortable" breathing exercises are both safe and effective when practiced in a controlled and supervised setting. Therefore, care must be taken to ensure end-user safety when porting to partially or fully technology-mediated designs (Tabor, Wilson & Bateman, 2019).

Discussion & Conclusions

The results of the current review study revealed that hypoxic training via breathing techniques and other methods has a major impact on hormonal responses and neurotransmitters levels. Lowering oxygen levels to a certain degree, individuals can stimulate the biomarkers that are responsible for neuroregeneration, higher cognition, positive emotions and consciousness expansion.

Although most studies outline the detrimental effects of hypoxia, it was found that under certain circumstances, hypoxia can a therapeutic strategy for anxiety, mood, and cognitive disorders. This review is in line with other studies (Navarrete & Mitchell, 2014; Navarrete et al., 2014) according to which *low dose hypoxia (modest hypoxia, few episodes) may be a safe and effective treatment with considerable therapeutic potential for multiple clinical disorders*. However, the use of hypoxia protocols should be coupled with reasonable safeguards (Mateika, 2014)

According to this review, hypoxic training has the following therapeutic benefits:

- Reduces anxiety hormones (i.e. cortisol) & hunger hormones
- Elevates hormones of pleasure (dopamine), relaxation (GABA, melatonin), socialization (oxytocin), happiness (endorphins), bliss (anandamide), painkilling (enkephalin), mood stabilization (serotonin).
- elevates growth factors
- Promotes nerve cell and new synapses growth and synaptic plasticity markers (i.e. hippocampal neurogenesis)
- has neuroprotective effects
- is associated with mitochondrial biogenesis
- Improves brain blood flow
- Regulates glucose metabolism
- Reduces oxidative stress and inflammatory markers
- Enhances antioxidant markers
- Improves brain oscillations of relaxation
- Improves mood (less tension, anger and depression)

- Reduces anxiety-like behaviors
- Improves cognitive performance (i.e. higher mental abilities (executive functions), better attention, short-term memory, reduced memory interference, better brain resilience)
- Alters human consciousness (i.e. trance, heightened euphoria, revelation, spiritual experiences, state of hibernation, steadiness of mind)
- paves the way for superhuman abilities (i.e. tolerance to the extreme pain, taking a breath per minute)

Hypoxia calms the mind, alters emotional states, heals pain, and fights infections. Not having enough oxygen for short periods has various benefits, including neuroplasticity, stem cell production, enhanced nitric oxide production, and increased EPO (Malshe, 2011).

Hypoxic training helps individuals to build a higher level of CO₂ tolerance. Increased tolerance to breathlessness results, in a greater amount of oxygen, freed to drive energy and repair (Zhou et al., 2008). CO₂ tolerance works as a natural protector for the acid keeping the body in a more alkaline state (Benner et al., 2018).

Low oxygen therapy can be achieved via various methods. According to this review low oxygen breathing techniques, chanting, localized hypoxia via blood flow restriction, hypoxia combines with exercise, and breathing in a paper bag can be effective ways to induce safe hypoxia. Digital technologies (i.e. wearable technologies, mobile apps, hypoxic breathing exercises apps, virtual reality breathing games) were found to play an important role in hypoxic training, tracking blood oxygen, recording heart rate variability, providing real-time biofeedback and alerts, informing the users about the time they hold their breath. Digital technologies also enhance motivation and keep users' attention on breathing.

Hypoxic training via breathing or other methods constitutes a tool for the regulation and upgrade of various physiological and neuropsychological processes. However, this 'tool' can be used by humans consciously and voluntarily, through Metacognition, as a means to take control of their physical, mental, emotional and spiritual wellness. Expansion of consciousness is to some degree under our control and requires training with the aim to develop the highest form of intelligence, known as Spiritual Intelligence (Drigas & Mitsea, 2020).

Metacognition in breathing refers to the (1) knowledge people have about the power of the breath, (2) awareness of their breathing status in real circumstances along with the parameters that affect their breathing, (3) attention and real-time observation of the breath, (4) conscious regulation of the breathing parameters (i. speed, depth, the rhythm of respiration, frequency, inspiration/expiration ratio, area of movement), (5) adaptations required to reach the desired breathing pattern, (6) recognition of those latent conditions (internal or external) that tend to provoke alterations in breathing, (7) decisions made to let unhelpful operations go away, (8) remembering to consciously breathe (Drigas & Mitsea, 2021;2022).

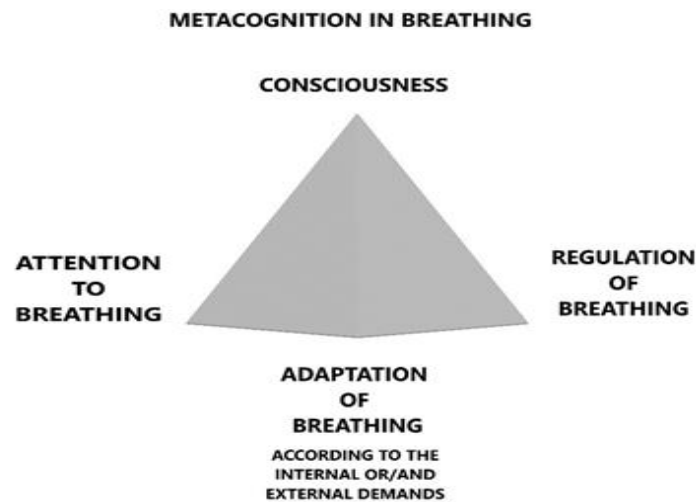


Fig. 1 Metacognition in breathing requires the ability to pay attention to breathing, regulate the appropriate breathing parameters and adapt to the desired breathing pattern. Metacognition in breathing can help people consciously and safely manipulate their breathing by moving themselves away from their comfort zone and exploring new pathways to rewire their brains and plumb the depths of their physical, cognitive, emotional and spiritual potential (Drigas & Mitsea 2020; 2021; 2022).

Our findings suggest that hypoxic training could be an effective intervention strategy with important *therapeutic benefits for people with learning and other disabilities (i.e attention-deficit/hyperactivity disorder, autism, motor impairments, depression, generalized anxiety disorder)* (Huber et al., 2018; Serebrovska et al., 2019). Future educators, therapists and families should be trained to appropriately apply simple hypoxic training exercises even in the educational context. For that reason, research into the physiological and neuropsychological mechanism that is affected by hypoxic training for individuals with learning or other disabilities is necessary.

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