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# The Hypoxia Training as a New Therapeutic Modality in the Treatment of Neurological Disorders - A Literature Review

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**ABSTRACT**

**Introduction:** Hypoxia training has emerged as a promising therapeutic approach for various neurological disorders. This systematic review examines the neuroprotective mechanisms and potential clinical applications of hypoxic training in neurology.

**Materials and Methods:** Literature review was conducted using databases such as PubMed, NCBI, and Google Scholar, with search terms including "hypoxia", "hypoxia training", "neuroprotection", "neurological disorders" and "physical activity".

**State of knowledge:** Controlled exposure to moderate hypoxia induces beneficial cellular and molecular adaptations in the nervous system. Key mechanisms include HIF-1 pathway activation, enhanced antioxidant responses, increased neuroplasticity, and serotonergic system modulation. These adaptations protect neurons against oxidative stress, excitotoxicity, and mitochondrial damage. Hypoxia training shows promise in treating neurodegenerative diseases, stroke, and spinal cord injury, improving cognitive, motor, and respiratory functions. Optimal protocols involve 10-16% oxygen exposure for 30-240 minutes, 3-7 times weekly for 2-6 weeks.

**Conclusions:** Hypoxia training offers a potential non-pharmacological approach to treating neurological disorders with minimal side effects when properly administered. Further research is needed to establish optimal protocols, identify novel biomarkers, and conduct larger clinical trials to fully understand its therapeutic potential in neurology.

**Keywords:** “Hypoxia”, “hypoxia training”, “neuroprotection”, “neurological disorders”, “physical activity”.

## INTRODUCTION:

Hypoxic training employs controlled low-oxygen environments to enhance physiological and neurological adaptations. Key methods include Live High-Train High, where living and training at moderate altitudes (2000–2500 m) boosts red blood cell production but may reduce training intensity. The widely adopted Live High-Train Low model preserves high-intensity training benefits while leveraging hypoxic adaptations. Variants like high-high-low (HHL) and artificial protocols using simulated altitude environments (e.g., nitrogen tents) provide flexible alternatives [1]. While prolonged exposure to continuous hypoxia yields promising

outcomes in athletes, shorter durations of hypoxic conditions have demonstrated greater efficacy in addressing neurological disorders.

Intermittent hypoxic training (IHT) is a therapeutic approach involving controlled, short-duration exposure to low oxygen levels, which contrasts with pathological hypoxia like that in sleep apnea [2,3].

IHT has gained attention for its ability to promote cerebrovascular health and mitigate vascular risk factors associated with neurodegenerative diseases, including Alzheimer's disease (AD). Studies suggest that IHT improves endothelial function, reduces arterial pressure, enhances nitric oxide (NO) bioavailability, and stimulates angiogenesis, thereby supporting cerebral blood flow and reducing oxidative stress. Additionally, IHT helps regulate oxidative and nitrosative stress by modulating the balance of NO production, potentially reducing neurotoxicity. These adaptations are associated with improved cognitive functions, including short-term memory and attention, particularly in populations with mild cognitive impairment. The benefits extend to systemic health, with evidence supporting its role in lowering blood pressure, enhancing glucose tolerance, and improving cardiovascular and respiratory functions. Furthermore, IHT fosters angiogenesis and neuroprotection, potentially through mechanisms like upregulated hypoxia-inducible factor-1 (HIF-1) and associated pathways [3,4].

Recent systematic reviews and meta-analyses show that controlled hypoxic training demonstrates enhanced antioxidant, anti-inflammatory, and cognitive benefits [5]. Hypoxic training offers promising potential for managing conditions such as Alzheimer's disease and Parkinson's disease. IHT, in particular, has exhibited promising results in improving cognitive function, motor recovery, and overall resilience to CNS injuries, offering a flexible and scalable strategy for clinical application [6]. This study comprehensively summarizes the benefits of hypoxic training for neurological diseases, emphasizing its potential as a non-pharmacological therapeutic approach.

**MATERIALS AND METHODS:**

A comprehensive review was conducted using databases such as PubMed, NCBI, and Google Scholar. The search process involved the use of keywords such as "hypoxia", "hypoxia training", "neuroprotection", "neurological disorders" and "physical activity" to identify relevant data. The data sourced from the searched articles was subjected to a detailed analysis in terms of methodology, results and importance to the topic to ensure the reliability of the study. Furthermore, only studies available in full-text format were utilized.

## STATE OF KNOWLEDGE

### 1. Neuroprotective effects and mechanisms of hypoxic training

Hypoxic training, especially when sustained over time, is gaining recognition for its neuroprotective benefits. These benefits result from a combination of cellular adaptations, including reduced oxidative stress, strengthened antioxidant defenses and enhanced neuroplasticity. Hypoxic conditions also affect the serotonergic system, which is critical for mood regulation and respiratory control [7]. This system helps adjust breathing patterns and responses to low oxygen levels. Prolonged hypoxic training enhances the body's ability to regulate respiration via serotonergic pathways, improving oxygen delivery during physical activity and lowering the risk of brain damage associated with hypoxia.

Exposure to low oxygen levels triggers the activation of hypoxia-inducible factor (HIF-1), a transcription factor that regulates the body's adaptation to hypoxia by stimulating the transcription of various genes. According to Semenza GL et al. these adaptations initiate protective mechanisms such as increased erythropoiesis and improved mitochondrial efficiency [8]. In the brain, HIF-1 activation supports cellular survival by influencing the expression of genes related to metabolism, inflammation, and cell protection, thereby exhibiting neuroprotective effects [8]. HIF-1 aids in neuronal survival and defends against oxidative stress and excitotoxicity, both of which are key contributors to neurodegenerative disorders [8]. It increases Vascular Endothelial Growth Factor (VEGF) levels, promoting angiogenesis and enhancing oxygen delivery to tissues, including the brain [9]. Additionally, Yuan M et al. observed that HIF-1 stimulates erythropoietin (EPO) production, improving the blood's oxygen-carrying capacity [10].

HIF-1 can stimulate the expression of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF), which play a crucial role in neuronal survival, growth, and differentiation, thereby contributing to neuroprotection and recovery following injury [11]. Therefore, hypoxic training enhances neuroplasticity, enabling the brain to reorganize and form new neural connections. Elevated levels of BDNF and other neurotrophic factors further support synaptogenesis and dendritic remodeling [12, 13]. Higher BDNF levels are also associated with improved cognitive function and memory.

Another benefit of hypoxic training is its ability to boost the production of antioxidant enzymes, which play a key role in neutralizing reactive oxygen species (ROS). Although prolonged hypoxia may initially trigger oxidative stress, the body gradually adapts by strengthening its antioxidant defense systems [11], offering additional neuroprotection against oxidative damage to brain cells. Research has demonstrated increased activity of key antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) [14,15]. SOD converts superoxide radicals into hydrogen peroxide and molecular oxygen, while catalase and GPx break down hydrogen peroxide into water, effectively neutralizing two harmful species [16]. These processes support the cerebroprotective and neuroprotective applications of Interval Hypoxic Training (IHT). Studies, such as those by Ryou MG et al., show that IHT protects the brain from glutamate excitotoxicity, mitochondrial damage, oxidative stress, and amyloid β accumulation [11]. Furthermore, intermittent hypoxic exposure has been linked to increased levels of anti-inflammatory markers and improved cognitive performance [17]. Studies have reported the decline in C-reactive protein(CRP), Tumor necrosis factor (TNF), IL-1β, IL-6 levels as a result of intermittent hypoxic exposure [18,19].

A different aspect worth mentioning is that hypoxia stimulates nitric oxide synthase (iNOS) activity [9]. Moreover, Lavier J et al. outlined that high-intensity hypoxic exercise also increases nitric oxide (NO) bioavailability [15]. NO facilitates vasodilation, enhancing cerebral blood flow and improving oxygen delivery to the brain during and after hypoxic training. Beyond this, nitric oxide exerts cytoprotective effects by regulating mitochondrial function and preventing neuronal apoptosis [20]. These protective effects are mediated through the activation of signaling pathways such as AMP-activated protein kinase (AMPK), which boosts mitochondrial biogenesis and energy production [21].

## 2. Neurodegenerative diseases - Parkinson's disease and Alzheimer's disease

Recent research has demonstrated promising results regarding the therapeutic potential of hypoxia training in neurodegenerative disorders. The moderate hypoxia induces evolutionarily conserved adaptive mechanisms that enhance neuronal viability and survival, particularly in conditions like Parkinson's disease (PD) and Alzheimer's disease (AD) [22]. The neuroprotective effects of hypoxia are attributed to its ability to ameliorate mitochondrial dysfunction and oxidative stress, which are fundamental pathological mechanisms in neurodegeneration [22].

In experimental models, chronic intermittent hypoxia (CIH) has shown significant effects on cognitive function and neuronal adaptation. Research utilizing rat models exposed to CIH (94% N2, 6% O2) for eight hours daily demonstrated notable changes in learning and memory capabilities [23]. While prolonged exposure to severe hypoxia may be detrimental, moderate hypoxia (10-16% O2) administered in controlled intervals has shown therapeutic potential [24]. Advanced imaging studies using laser scanning confocal microscopy have revealed that hypoxia induces significant changes in neuronal morphology, including alterations in cytosolic calcium levels and RNA distribution [25]. These cellular adaptations may contribute to the neuroprotective mechanisms observed in clinical settings. Furthermore, research has shown that brief periods of mild hypoxia (10% O2) can improve mitochondrial function, particularly complex 1 respiration and ATP-related oxygen consumption [26].

The therapeutic application of hypoxia requires careful consideration of dosing and timing. Clinical studies suggest that low-dose intermittent or continuous hypoxia, administered in 30-240 minute sessions, produces optimal beneficial effects, especially when combined with motor-cognitive training [24]. This approach has shown particular promise in addressing the pathophysiological mechanisms underlying PD, where hypoxic conditioning may enhance neuronal resilience through activation of adaptive cellular responses [22]. Recent systematic reviews have highlighted that 75% of human studies indicate cognitive and neurological benefits from controlled hypoxia exposure [24]. The molecular mechanisms underlying these improvements include enhanced production of neurotrophic factors, modulation of inflammatory responses, and activation of cellular repair pathways [22]. These findings suggest that hypoxia training, when properly administered, may represent a viable therapeutic approach for managing neurodegenerative conditions [26].

While direct studies on hypoxia training in AD are limited, research has explored related areas. A 2023 study investigated the use of genetic algorithms and LightGBM for modeling acetylcholinesterase inhibitors in AD drug discovery, achieving high accuracy in predicting potential compounds [27]. This approach could accelerate the identification of promising candidates for AD treatment. Additionally, a study examining the relationship between sleep fragmentation, AD biomarkers, and cognitive impairment in obstructive sleep apnea (OSA) patients without dementia revealed interesting connections [28]. The research found that sleep fragmentation's impact on cognition was mediated by amyloid-β42 (18.25% to 30.6%), phosphorylated tau (24.36% to 32.3%), and complement protein C5b-9 (30.88% to 60.7%) [28]. A cohort study in South Korea explored the bidirectional association between PD and OSA, a condition characterized by chronic intermittent hypoxia [29]. The study found that OSA patients had a 1.54-fold higher incidence of PD compared to non-OSA controls, while

PD patients showed a 1.92-fold higher incidence of OSA compared to non-PD controls [29]. These findings suggest a complex interplay between hypoxia-related conditions and neurodegenerative disorders.

A randomized controlled trial protocol published in 2024 aims to investigate the effects of intermittent hypoxia in PD [22]. This study will provide valuable insights into the therapeutic potential of controlled hypoxia exposure for PD patients. The emerging evidence suggests that carefully controlled hypoxia training may offer therapeutic benefits for neurodegenerative disorders. However, further research is needed to establish optimal protocols and fully understand the underlying mechanisms.

## 3. Stroke and Cerebrovascular Disorders

In the initial stage following an ischaemic stroke, the inflammatory response plays an essential role, limiting damage within the ischaemic area. However, chronic inflammation that occurs afterwards leads to a recurrence of the stroke and inhibits the healing process. Furthermore, another significant factor is the formation of reactive oxygen species (ROS) during the ischemic period, which results in cellular damage. The cells that participate in the inflammatory process include microglia, which exhibit two distinct phenotypes. Type 1, which phagocytoses damaged cells and secretes cytokines, enhancing the inflammatory response; and Type 2, which also removes dead cells but limits the inflammation. The study [30] investigated the potential of intermittent hypoxia training (IHT) to promote the polarization of microglia from the M1 to the M2 phenotype. This was conducted on cell cultures. The research demonstrated that normobaric intermittent hypoxia training (IHT) protects microglia from a number of adverse effects associated with oxygen–glucose deprivation (OGD) during stroke, including cell death, and promotes a polarization towards an M2 phenotype. Additionally, IHT enhances microglial phagocytic capacity and reduces ROS levels. The authors suggest that these changes facilitate the healing process of the ischemic area. Another study [31] demonstrated that the selective removal of microglia from the mouse brain increased the infarct size during stroke by 60%, indicating the significance of these cells. Researchers emphasise [30] that IHT could play a pivotal role in the recovery process among ischemic stroke patients.

A double-blind randomised controlled trial [32] included 100 healthy patients, who were divided into two groups. The intervention group undertook intermittent hypoxia training (IHT), which consisted of breathing for 10 minutes in air with a 13% oxygen concentration, and then for 5 minutes in normoxic air. This cycle was repeated four times, with sessions held every day for five days. The control group breathed normoxic air throughout the entire study. The following measurements were taken:

- Transcranial Doppler (TCD).
- Cognitive performance was assessed using the variety of tests: the Digit Span Test (DST), a variation of the Digit Span Test (DSTR), the Trail Making Test (TMT), and the Stroop Colour-Word Test (SCWT).
- Cerebral perfusion pressure (CPP): The measurement of blood pressure and intracranial pressure (ICP) was conducted noninvasively. The formula for estimating mean arterial pressure (MAP) was: 1/3 systolic blood pressure (SBP) + 2/3 diastolic blood pressure (DBP), and the formula for calculating CPP was: MAP - ICP.
- Cerebral tissue oxygen saturation ($ScO_2$) was determined by near-infrared spectroscopy (NIRS).

The study demonstrated that peak systolic blood flow velocity (PSV), mean blood flow velocity (MFV) and cerebrovascular conductance index (CVCi) were elevated, while cerebrovascular resistance index (CVRi) was lower among the IHT group following the intervention. A series of cognitive performance showed no differences between the intervention and control groups with regard to the DST, DSTR, TMT and SCWT. No differences were observed in MAP and ScO2 measurements after the training. Assessments showed that IHT had a modest positive impact on cerebral blood flow, however according to the authors those changes could be clinically significant for patients who suffered from cerebrovascular diseases such as ischemic stroke, Alzheimer's disease and vascular dementia. It was demonstrated that IHT improves cerebral blood flow, increases blood flow velocity, cerebrovascular conductance, and decreases cerebrovascular resistance among healthy patients.

In a study conducted by Gregory EP Pearcey et al. [33], the impact of acute intermittent hypoxia (AIH) on upper limb strength and the safety of the intervention among patients who had suffered from an ischaemic stroke was examined. The acute intermittent hypoxia (AIH) consisted of alternating periods of breathing air with a reduced oxygen concentration and then normoxic air. The intervention consisted of four sessions, each with 15 cycles. The oxygen concentration was reduced by 4% with each session, beginning at 21% in the initial session and decreasing to 9% in the final session. Ten participants completed all procedures. The measurements included electrocardiogram (ECG), heart rate (HR), troponin levels, oxygen saturation, neurological assessment, grip strength by hand dynamometer and magnetic resonance imaging (MRI) (prior to the intervention). The research

revealed that AHT improved volitional strength of the hand and elbow musculature by 5% and 13% respectively, while being well tolerated by patients.

Many researchers emphasize that IHT has a beneficial impact on hypertension, obesity, diabetes and dyslipidemia which are common risk factor of ischemic stroke [34]. A number of studies revealed that IHT can improve brain and heart's defensive mechanism against a ischemic injury in rodents, reduce inflammation, promote neovascularization, neurogenesis and neuroplasticity.

## 4. Cognitive Function and Mental Health

The role of physical activity in improving cognitive functions and its impact on mental health are becoming the subject of an increasing number of studies worldwide. Subsequent publications exploring the mechanism of physiological processes occurring under the influence of physical activity and affecting the maintenance of intellectual fitness are multiplying and providing new, valuable information [35].

In one of these studies, by Kerr et al., older adults who regularly participated in 30 minutes of moderate- to vigorous-intensity PA required only 61 seconds to complete a cognitive test, which is 15% faster compared to the average of 72 seconds [36].

Numerous meta-analyses have confirmed that physical exercises have the most significant impact on memory, information processing speed, and executive functions. Neuroimaging has shown that higher levels of physical fitness are associated with greater gray matter volume, better white matter integrity, and higher cerebral blood flow [37].

Increasing attention is being paid to the role of hypoxia training as a method bringing benefits in terms of cognitive functions and mental health.

Intermittent hypoxia training (IHT) shows potential in improving cognitive functions in older adults with mild cognitive impairment (MCI) [38]. In a pilot study by H. Wang et al. conducted on patients with MCI, an 8-week IHT program consisting of alternately breathing 10% O2 and room air for 5 minutes each, for 8 cycles per session, 3 sessions per week for 8 weeks, proved effective in improving cognitive functions. It improved short-term memory and attention test scores. Specifically, Mini-Mental State Examination (MMSE) scores increased from $25.7 \pm 0.4$ before IHT to $27.7 \pm 0.6$ after IHT ($P=0.038$), and Digit Span test scores improved from $24.7 \pm 1.2$ to $26.1 \pm 1.3$ ($P=0.047$) [3]. A trend towards improvement in California Verbal Learning Test scores was also observed ($P=0.102$), although it did not reach statistical significance [3].

Studies have shown that exercises performed under hypoxic conditions can improve cognitive functions, including attention and executive functions. A meta-analysis by M. Jung et al. demonstrated that performing exercises under hypoxic conditions has a statistically significant effect on improving cognitive functions (SMD = 0.30, 95% CI: 0.14-0.45, $I^2 = 54\%$, $p < 0.001$) [5]. Exposure to hypoxia without exercise, on the other hand, may impair attention abilities (SMD = -0.40), executive functions (SMD = -0.18), and memory (SMD = -0.26), but improve information processing (SMD = 0.27). These effects were moderated by various factors, such as age, type of cognitive task, type and intensity of exercise, and level of hypoxia [39].

The ALTIBRAIN project aims to further and thoroughly test this concept [40]. The goal of the study is to evaluate the impact of cognitive training under hypoxic conditions on cognitive functions and neuroplasticity in healthy individuals and patients with affective disorders. The study will involve 120 healthy volunteers and 60 patients with affective disorders in remission. Participants will be randomly assigned to groups receiving cognitive training under hypoxic conditions (12% O2) or normoxic conditions (20% O2) for 3.5 hours daily over 3 weeks. The primary endpoint will be the change in a composite cognitive score, including tests of attention, memory, and executive functions. Assessments of cognitive functions, psychosocial functioning, and quality of life will be conducted at baseline, after treatment completion, and one month later. fMRI studies will be performed at baseline and one month after treatment completion, while PET scans using [11C]UCB-J will be conducted post-treatment to quantitatively assess synaptic vesicle glycoprotein 2A (SV2A) [40].

Researchers anticipate that cognitive training under hypoxic conditions will lead to lasting improvements in cognitive functions, accompanied by changes in hippocampal volume and function as well as presynaptic density in the hippocampus and prefrontal cortex [40].

## 5. Spinal Cord Injury

Hypoxia training shows promise as a potential therapeutic method for patients with spinal cord injury (SCI). Acute intermittent hypoxia (AIH) has been demonstrated to induce respiratory motor plasticity in rodent spinal cords, and repeated sessions of such hypoxia may restore respiratory function in individuals with SCI. This was investigated in a study by Sutor et al. [41], who recruited 17 individuals with chronic spinal cord injury (more than six months post-injury). The protocol involved 15 cycles of brief, one-minute episodes of acute intermittent

hypoxia (hypoxia: 10.3% $O_2$; sham: 21% $O_2$), interspersed with 1.5-minute intervals of breathing normal room air (21% $O_2$).

Baseline $SpO_2$ levels were 97.2 ± 1.3% and remained stable during sham experiments. During hypoxic episodes, $SpO_2$ decreased to 84.7 ± 0.9% and returned to baseline levels during normoxic intervals. No changes were observed compared to baseline values after sham treatment. However, greater increases in maximum inspiratory pressure (MIP) were noted following AIH compared to sham treatment (median values: +10.8 $cmH_2O$ vs. -2.6 $cmH_2O$, with a 95% confidence interval), reflecting a moderate Cohen's effect size (0.68). Other respiratory parameters, including P0.1, MEP, and FVC, did not change post-AIH. A single session of AIH enhanced maximum inspiratory pressure generation but did not affect other respiratory functions in adults with spinal cord injury.

Trumbower et al.[42] also investigated the effects of hypoxia on patients with SCI. They demonstrated that a single exposure to 15 episodes of AIHimproved motor performance in the lumbosacral region and enhanced maximum voluntary plantar flexion torque generation in individuals with chronic, incomplete spinal cord injury. The improvement in leg strength was associated with increased activation of the gastrocnemius muscle. Notably, muscle strength gains persisted for more than four hours in 4 out of 10 participants, suggesting the potential for prolonged effects.

Navarrete-Opaza et al. [43] conducted a randomized controlled trial on patients with spinal cord injury and demonstrated that daily intermittent hypoxia combined with body weight-supported treadmill training significantly enhanced walking speed, as indicated by reduced times in the 10-meter walk test on day 5 compared to baseline. Endurance, assessed by increased distances in the 6-minute walk test, also showed significant improvement by day 5. Additionally, administering intermittent hypoxia three times per week sustained the walking speed improvements achieved during daily sessions and further increased walking endurance, with these benefits persisting for up to a two-week follow-up period.

Sandhu et al. [44] conducted a randomized, placebo-controlled, double-blind, crossover study involving a single session of AIH or sham AIH in 14 individuals with chronic, incomplete cervical spinal cord injury (SCI). They observed that a single AIH session improved bilateral grip and pinch strength, with the effects peaking approximately three hours post-intervention. The researchers propose that these outcomes are attributed to AIH-induced rapid plasticity and enhancement of volitional somatic motor output.

How can we enhance the effectiveness of AIH-based training? Hayes et al. [45] demonstrated in their study that daily AIH combined with overground walking significantly improves walking speed and endurance in individuals with chronic, incomplete spinal cord injury. A total of 19 participants completed their randomized, double-blind, placebo-controlled crossover trial.

## 6. Therapeutic Protocols of hypoxia

To make hypoxia an effective method for supporting the treatment of neurological diseases, it must be used sensibly and according to specific protocols. Optimal therapy appears to involve using 10-16% oxygen, repeated 3-7 times per week for 2- 6 weeks, in sessions lasting 30- 240 minutes. These sessions can consist of cycles or be continuous. However, excessively long hypoxia sessions exceeding 6 hours may cause more harm than benefit [24].

It is worth noting that the therapeutic effect of induced hypoxia depends not only on oxygen concentration but also on pressure, which distinguishes between normobaric and hypobaric hypoxia [32]. For example, a study conducted by Schneider SR et al. showed that hypobaric hypoxia contributes to a greater reduction in saturation levels than normobaric hypoxia [46].

Another study confirms that hypoxia should be applied with intervals, i.e., alternating 2-minute periods of hypoxia and 2-minute breaks, all under normobaric conditions. There should be 12 hypoxia-break cycles per day, and this therapy should last several days. It is also suggested to apply hypoxia for 30 minutes daily for about 10 days [47].

In the study [48], cycles consisting of periods of hypoxia and normoxia (4 minutes each) were applied, with a total of 5 cycles, achieving a minimum saturation of 90%. However, no statistically significant changes were observed in the examined erythropoietin levels and hemoglobin mass in red blood cells.

In another study, which noted a positive effect of hypoxia on reducing blood pressure, a protocol involving 12 cycles of 2-minute normoxia and 2-minute hypoxia periods over 15 days was applied [49].
There are also views suggesting that hypoxia can be applied in cycles alternating with hyperoxia, rather than normoxia, and that the hypoxia-hyperoxia method can be used both during physical exercise and at rest. Normoxia involves supplying 21% oxygen through a mask, while hyperoxia involves 30- 40% oxygen [50].

In a study conducted by Afina AB et al., the mentioned method of intermittent hypoxia and hyperoxia was applied using a breathing therapy device. After a period of administering a gas mixture with reduced oxygen content, when the patient’s saturation reached the intended minimum, the device supplied a gas mixture with increased oxygen content, restoring saturation to normal values within a few minutes. This therapy was applied

for 3 weeks, from Monday to Friday, for 40- 45 minutes daily. Participants showed reductions in total cholesterol, triglycerides, and high-sensitivity C-reactive protein (CRPhs). This suggests that such a therapy protocol may be effective in supporting the treatment of many diseases [51].

Induced hypoxia is a promising tool for supporting the treatment of various diseases, including neurological disorders, but its efficacy and safety depend on a well-planned protocol. Different strategies, such as applying cycles of hypoxia and normoxia or hypoxia and hyperoxia, yield diverse therapeutic effects, suggesting the potential for wide applications of this method.

Research indicates that the key factors influencing therapeutic outcomes include the proper adjustment of parameters such as oxygen concentration, session duration, and the number of cycles.

Although initial results are encouraging and show positive effects of hypoxia in various areas, further research is needed to resolve existing uncertainties, determine the role of induced hypoxia as an adjunct therapy in medicine, and develop optimal treatment protocols

## 7. Safety Considerations and Clinical Efficacy

Hypoxic training in the treatment of neurological disorders raises many questions: is it safe for patients with neurological problems? What potential side effects might this therapy have? What protocols and precautions should be implemented to minimize the risk of side effects? Clinical studies confirm that properly conducted hypoxic training is safe. Key findings indicate improvement in the neurological condition of stroke patients, enhancement of cognitive performance in older adults, reduction of inflammatory markers in various diseases, and minimal adverse effects when appropriate protocols are followed.

According to a systematic review by Damgaard V. [24], which included 58 studies, 8 of which were conducted on humans with various CNS disorders such as traumatic brain injury, mild cognitive impairment, and healthy individuals, 6 of these studies (75%) showed beneficial effects of moderate hypoxic training. In the remaining two studies (12.5%), no effectiveness was found, and in one (12.5%), negative effects were observed. The best results were obtained with normobaric exposure to hypoxia at moderate intensity (10-14% O2) in short sessions lasting 30–90 minutes, repeated over 2–12 weeks, often combined with physical exercises [52]. Moderate doses of hypoxia improved cognitive and motor functions and increased neuroplasticity markers, such as neurotrophins and EPO levels. The studies suggest that intermittent hypoxic training may be effective, especially when combined with motor-cognitive rehabilitation. A synergistic effect of exercise was also observed, which further increased neuroplasticity. However, studies on humans were prone to high risk of bias due to small sample sizes, lack of randomization, and inconsistent protocols. The safety of moderate hypoxic training has been confirmed when appropriate protocols are followed, although a small number of adverse effects were observed, mainly in studies involving higher doses or intensity of hypoxia. In summary, moderate, short-term exposure to hypoxia appears to be safe and potentially effective in improving cognitive and neurological functions. However, larger, well-designed randomized trials are needed for a definitive evaluation of its effectiveness and safety [24].

Other human studies indicate that moderate hypoxia (9–16% O2) and a small number of cycles per day (3–15 episodes) bring therapeutic benefits and are safe. In contrast, intense hypoxia (2–8% O2) and a greater number of cycles (up to 2400 per day) may lead to pathological effects [52]. It is suggested that "low-dose" IHT, applied under moderate conditions, could be an effective therapeutic method, especially in a clinical context. Intermittent hypoxia does not lead to secondary ventilation reductions, making it more beneficial than prolonged hypoxia. These mechanisms are associated with respiratory system adaptation, making moderate hypoxic exposures safer and more effective. IHT protects the brain from damage related to glutamate excitotoxicity, oxidative stress, mitochondrial damage, and the accumulation of β-amyloid [9]. Moderate IHT improves cognitive functions such as short-term memory and attention, particularly in older patients with mild cognitive impairment (MCI). There are also suggestions that IHT may help in treating Parkinson's disease [53] and depression [54]. Human studies confirm the therapeutic potential of IHT in medical practice.

Establishing a universal protocol for Intermittent Hypoxia Conditioning (IHC) is currently not possible, as it should be tailored to the individual needs of the patient and the specific clinical context. The effects of IHC depend on the disease, coexisting conditions, medications, and the patient's status, so a detailed analysis of risks and benefits is necessary. It is crucial to develop standardized guidelines that take these variables into account, allowing for more effective treatment. Combining IHC with other methods, such as pharmacotherapy or physical exercises, may enhance its effects and provide a more comprehensive therapeutic approach. Interdisciplinary strategies could contribute to the creation of innovative treatment methods. Further research into the molecular mechanisms of IHC could help improve this therapy and adapt it to the individual needs of patients. Large, randomized clinical trials are also necessary to confirm the effectiveness and safety of IHC in various populations and diseases. The results of such studies may solidify the role of IHC in standard medical practice. In conclusion, IHC has great potential, but its application requires scientific grounding and precise adaptation to the patient's specifics [32].

## 8. Future Perspectives and Research Directions

Hypoxic training as an innovative therapeutic modality for treating neurological disorders remains an area of intense research, offering a wide range of potential development directions. In the future, it will be crucial to adapt training protocols to the individual needs of patients. The development of personalized programs that take into account specific clinical features, disease progression, and the body's adaptive capabilities may help increase the effectiveness of therapy [9].

Cognitive impairments are prevalent in many neuropsychiatric disorders, significantly hindering the recovery process and limiting psychosocial functioning. One of the key challenges in developing effective and long-lasting therapies to improve cognitive functions is the incomplete understanding of the mechanisms underlying sustained neuroplasticity. However, emerging evidence suggests potential benefits of moderate hypoxia training, both in human studies and animal models, for enhancing cognitive functions [40].

Future research should focus on overcoming the limitations of current biomarker approaches in evaluating the neuroprotective benefits of intermittent hypoxia. Although the selection of biomarkers is extensive, their capacity to offer a complete understanding of the underlying neuroprotective mechanisms remains constrained [55,56]. This is also the case in Parkinson's disease (PD), where intermittent hypoxia is a promising, low-cost, and easily implementable non-pharmacological strategy. However, its potential remains limited due to the scarcity of studies conducted on small participant groups and the use of neurological biomarkers that are restricted to brain-derived neurotrophic factor (BDNF) [55]. The study conducted by Daalen et al. [22] significantly expanded the understanding of the following biomarkers: neurofilament light chain (NfL), which is associated with motor progression in PD and is reduced through exercise; clusterin, a potential regulator of exercise effects that may positively influence neuroinflammation and be inversely correlated with cognitive function; glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1), markers of acute brain injury; and BDNF, which can be upregulated by both hypoxia and exercise.

Alzheimer's disease (AD) is a degenerative neurological disorder in which traditional pharmacological therapies are largely ineffective and associated with numerous side effects, making non-pharmacological therapies a promising alternative. Hypoxia, one of the pathogenic factors in AD, affects processes such as amyloid-beta metabolism, tau phosphorylation, neuroinflammation, oxidative stress, as well as mitochondrial and synaptic dysfunction [57,58]. Hypoxia-targeted treatments, including oxygen therapy, may improve symptoms and risk factors of Alzheimer's disease (AD), as well as positively influence pathological changes associated with the disease, such as amyloid-beta metabolism and mitochondrial function. Future research on oxygen therapy could contribute to the development of more effective treatment methods for AD [59].

The future research potential of this method includes the development of neuroprotective therapies, such as targeted modulation of molecular pathways like SIRT1 and autophagy to protect brain tissue, the use of exosomes from stem cells as therapeutic carriers, and the application of transcranial stimulation (tDCS) in the treatment of ischemic stroke effects. Additionally, the development of models reflecting the functioning of the HPA axis to better predict therapy outcomes is essential, with intermittent hypoxic training emerging as a promising strategy for preventing neurodegeneration and supporting the aging brain [9,60].

## CONCLUSIONS

Hypoxia training demonstrates significant potential as an innovative therapeutic approach for neurological disorders. Research indicates beneficial effects of controlled exposure to moderate hypoxia, including activation of neuroprotective pathways, enhanced antioxidant responses, and increased neuroplasticity. Particularly promising results have been observed in Parkinson's disease, Alzheimer's disease, stroke, and spinal cord injury, where hypoxia training has contributed to improvements in cognitive, motor, and respiratory functions. Optimal therapeutic protocols typically involve exposure to 10-16% oxygen in sessions lasting 30-240 minutes, repeated 3-7 times per week for 2-6 weeks. The safety and efficacy of the therapy depend on precise adjustment of parameters to individual patient needs. Future research should focus on developing personalized protocols, identifying novel biomarkers, and conducting larger, randomized clinical trials to fully understand the mechanisms of action and therapeutic potential of hypoxia training in neurology.

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