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Review

Sleep-Disordered Breathing and Central Respiratory Control in Children: Comprehensive Review

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Abstract: Background/Objectives: Sleep-disordered breathing (SDB) is a primary concern in children's health. Research suggests repeated oxygen drops during sleep—common in SDB—may harm the brainstem's breathing control centres. This damage likely occurs through oxidative stress, inflammation, and cell death, which weaken the brain's ability to regulate breathing. Over time, these effects could lead to functional changes (e.g., disrupted chemical signalling) and physical damage in critical brain regions, creating a cycle of unstable breathing. However, much of this evidence comes from animal or lab studies, leaving gaps in our understanding of how these mechanisms work in humans. This review synthesises existing research on how breathing disruptions during sleep—particularly episodes of intermittent hypoxia—affect the brain's ability to control respiration in children and adolescents. **Methods:** We analysed studies from medical databases PubMed, Scopus and WebOfScience, focusing on how SDB (obstructive or central sleep apnea) impacts the brain's respiratory centres in young populations. Animal studies and research involving children on mechanical ventilation were excluded to focus on natural sleep patterns. **Results:** After removing duplicates, 53 studies remained. Finally, 8 studies were reviewed, 2 focused on obstructive sleep apnea (OSA), where breathing is blocked by airway collapse; 6 examined central sleep apnea (CSA), where the brain fails to signal breathing, including studies on newborns (3) and infants (3). In addition, three studies on children with genetic conditions, like Down syndrome, Prader-Willi Syndrome and Pierre Robin sequence, were included. The findings suggest that repeated oxygen dips during sleep may harm the brainstem's respiratory control areas, especially during critical developmental stages. This damage could lead to long-term issues, such as unstable breathing, cardiovascular strain, or neurological problems. However, most studies only captured the immediate effects of low oxygen, leaving uncertainty about permanent harm due to a lack of long-term follow-up. **Conclusions:** Repeated oxygen deprivation during sleep appears to damage the brainstem and disrupt breathing regulation. However, small study sizes and short observation periods limit the strength of these conclusions. Future research should use advanced imaging tools to clarify long-term risks, develop effective treatments and track children over extended periods. More significant, longer-term studies are urgently needed to guide clinical care for vulnerable populations.

Keywords: Central respiratory; central sleep apnea; children; infant; neurorespiratory; obstructive sleep apnea; sleep-disordered breathing.

1. Introduction

Sleep-disordered breathing (SDB), including Central Sleep Apnoea (CSA) and Obstructive Sleep Apnoea (OSA), is a significant health issue in children and teens. It disrupts the balance between the nervous and respiratory systems, potentially hindering healthy development [1]. In OSA, repeated breathing pauses occur during sleep due to blocked airways or faulty brain signals controlling respiration [2].

Low oxygen levels can harm the brainstem's respiratory centres, especially in developing children or those with genetic risks. This damage includes imbalances in brain chemicals, malfunctioning oxygen sensors, and structural changes like a buildup of scar-like brain cells (astrogliosis) [3] [4]. Studies also show abnormal brain development in kids with OSA, affecting areas critical for breathing [5].

The brainstem contains specialised cells that act as oxygen sensors, activating breathing when oxygen levels fall [6]. During abrupt oxygen shortages, the body responds in two distinct phases: an initial surge in breathing effort, followed by a rapid decline as the brainstem's regulatory circuits become overwhelmed. This pattern mirrors a system pushed to its limits—briefly compensating before faltering under strain [7–9]. Over time, repeated oxygen deprivation can harm breathing, heart health [10], and brain function [9] [11]. In adults with OSA, brain scans reveal damage to white matter—the "wiring" connecting areas like the limbic system, cerebellum, and cortex [12] [13].

While SDB research has advanced, scientists still struggle to understand how the brainstem controls breathing in children. Specifically, two areas—the medulla and pons—play a critical role in maintaining breathing rhythms during sleep and adapting to chemical cues like oxygen and carbon dioxide levels in the blood. These regions act like a "breathing control centre," fine-tuning respiration based on the body's needs, but much about their function in kids remains unclear [14] [15]. However, in kids with SDB, repeated breathing pauses may damage these areas, making them less responsive to oxygen changes or airway shifts [16] [17]. For example, chronic low oxygen in OSA may blunt the brainstem's oxygen sensors, worsening breathing instability [18].

Emerging research links SDB's body-wide effects—like poor brain oxygenation and irregular heart function—to harmful changes in brainstem regions in pediatric patients [19] [20]. These changes might explain why some children still struggle with SDB even after surgery to fix airway blockages [21] [22]. This highlights the need to differentiate between physical airway issues and nervous system dysfunction when treating SDB [23] [24].

Aim of the Study

This study reviews the existing literature on the link between SDB, intermittent hypoxaemia, and the function of the neurological centres that regulate respiration during sleep in children and adolescents.

2. Materials and Methods

We searched three major databases—MEDLINE (PubMed), Scopus, and Web of Science—for English-language studies published from their earliest records up to January 20, 2025. Custom search terms were tailored for each database, combining keywords:

Inclusion terms: sleep-disordered breathing, sleep apnea, obstructive sleep apnea, upper airway obstruction paired with neurorespiratory, central respiratory, medullary respiratory, pontine respiratory and age-related terms (children, infants, adolescents).

Exclusion terms: case reports, animal studies, mechanical ventilation techniques, and studies focused on adults or elderly populations.

Study Selection Process

After removing duplicates, 53 studies remained. Further exclusions were made based on: 7 case reports/series, 5 non-English studies, 3 animal studies, 2 conference abstracts, 9 review articles, 6 unrelated topics. This left 12 studies for evaluation, plus 9 additional studies focused on syndromes. After deeper analysis: 7 studies were unrelated to the topic, 1 study involved adults, 1 was a review of syndromic cases.

The remaining studies formed the basis of our analysis.

3. Results

Table 1 provides details on two studies investigating OSA. One notable study, a crossover trial involving 10 school-aged children [20], demonstrated that exposure to high altitude exacerbates the severity of SDB. Specifically, the study reported an increased AHI, worsening oxygenation (SpO₂), increased sleep fragmentation, and heightened cardiovascular stress, as indicated by elevated heart rate [20]. The findings indicate that the low-oxygen conditions of high-altitude environments (hypobaric hypoxia) might interfere with the brain's ability to regulate breathing—specifically disrupting communication between the medulla and pons, key brainstem regions that act as the body's "breathing command centre." Surprisingly, despite the strain on the body, the study found no apparent harm to children's brain function or heart health [20]. Researchers speculate this could be because the children were only exposed briefly or because their bodies adapted temporarily to protect them.

While the study confirmed physical changes like reduced oxygen levels and fragmented sleep, it did not detect clear signs of long-term neurological or cardiovascular damage. This gap between observed stress and visible harm raises questions about whether children's resilience or the study's limitations (like short-term observation) masked subtle effects. This discrepancy suggests that children may possess transient adaptive mechanisms that mask potential subclinical neuronal damage [20]. Furthermore, the value of monitoring Tissue Oxygenation Index (TOI) and Pulse Transit Time (PTT) in children [19] supports using portable, multimodal assessment tools to evaluate SDB severity and central nervous system (CNS) involvement in real-world settings.

Another study examined a cohort of 60 children aged 3 to 12, revealing that central respiratory events during non-REM (NREM) sleep led to reductions in cerebral oxygenation like those observed in obstructive events [19]. These episodes coincided with changes in peripheral blood pressure and heart rate, suggesting that central apneas might lead to brief periods of cerebral hypoxia [19]. This observation supports previous findings showing that intermittent hypoxia, common in SDB, can harm neurological development and cardiovascular health, even without obvious immediate symptoms. The PTT, a non-invasive measure of autonomic activity, significantly drops during breathing disruptions, reflecting increased sympathetic nervous system activity [19]. Similarly, the TOI falls during apnea events, showing reduced oxygen supply to tissues and underscoring how respiratory regulation affects overall blood flow [19]. These physiological markers provide insight into how central respiratory control dysfunction can trigger a cascade of autonomic and cardiovascular responses mediated by brainstem nuclei and higher cortical networks. Finally, the finding that central and obstructive respiratory events similarly reduce cerebral oxygenation [19] underscores the need for a shift in perspective regarding SDB management.

Table 1. Summary of included studies and key findings.

Author(s) (year of publication)	Design	Subjects	Methods	Results	Conclusions	Relazione con Neurologia e SDB/OSA
Hughes BH	Crossover study	10 children	Home PSG (high	Elevated AHI,	High altitude	Neurophysiological impact;

(2017) [20]		(4.9 to 12.7 years; 60% males); high altitude; SDB	altitude) vs laboratory PSG (low altitude) comparison	worse oxygenation, increased heart rate, and sleep fragmentation at high altitude (AHI 10.95/h, ODI 19.5/h) vs low altitude (AHI 2.4/h, ODI 3.6/h)	worsens the symptoms of SDB; Home tests more indicative of severity	Altitude; Severity of SDB; Major neurological impairment
Tamanyan K (2019) [19]	Observational study	60 children (3-12 years) with suspected SDB	PSG, detailed analysis of cerebral and peripheral oxygenation, blood pressure, heart rate changes	Greater variation in cerebral oxygenation during central respiratory events compared to obstructive ones, especially in NREM sleep	Central respiratory events affect cerebral oxygenation like obstructive events	Significant impact of CA on neurocognitive and cardiovascular health like obstructive events
Authors and Date	Apneas	Apnea Assessment Methods	Impact on Respiratory Centers and CNS	Evaluation of Respiratory Centers and CNS	Clinical Implication	Conclusions
Hughes BH (2017) [20]	Obstructive and Central Apnea	AHI, SpO2, CAI, CHI	Altitude exacerbates the severity of SRBDs. It influences central breathing control	AHI, SpO2, Heart Monitoring	High altitude increases respiratory interruptions and lowers SpO2, impacting	Environmental factors such as altitude critically influence the severity of SRBDs and their physiological

			and cardiovasc ular stress.		CNS and cardiovasc ular.	impact on the respiratory and cardiovascula r systems. Need for specific strategies for altitude.
Tamany an (2019) [19]	Central and Obstructi ve Sleep Apnea	TOI, PTT, HR Monitor ing	Changes in TOI, PTT, and HR during respirator y events reflect the role of the CNS and the autonomic nervous system in regulating cardiovasc ular and respirator y responses.	TOI, PTT, HR monitorin g during sleep, differentia tion between REM and NREM sleep	Significant physiologi cal changes do not result in clinically meaningfu l findings, underscori ng the complexity of diagnosis and treatment based on physiologi cal responses alone.	Need for more refined methodologie s to differentiate the impacts of various types of respiratory events on physiological parameters and implications for respiratory control and CNS in children.

Legend: AHI, Apnea-Hypopnea Index; CA, Central Apnea; CAI, Central Apnea Index; CHI, Central Hypopnea Index; CNS, Central Nervous System; HR, Heart Rate; NREM, Non-Rapid Eye Movement; ODI, Oxygen Desaturation Index; OSA, Obstructive Sleep Apnea; SpO₂, Oxygen Saturation; PSG, Polysomnography; PTT, Pulse Transit Time; REM, Rapid Eye Movement; SDB, Sleep-Disordered Breathing; SRBD, Sleep-Related Breathing Disorders; TOI, Tissue Oxygenation Index.

Table 2 provides an overview of studies examining the effects of predominantly central SDB on sleep physiology in children, including three studies focusing on infants and three on older children, all within specific clinical contexts.

A histopathological investigation of the medulla oblongata in newborns showed notable changes in dendritic spine density within respiratory control centres before and after birth [25]. These results emphasise the importance of neuronal maturation in establishing robust respiratory regulation, highlighting how early susceptibility to SDB may stem from the developmental progression of these critical neural networks [25].

An experimental approach was proposed to counteract central respiratory insufficiency in neonates, using a combination of sensory stimuli, including light exposure and controlled modulation of O₂ and CO₂ levels, to stabilise breathing during sleep [26]. While promising, this technique requires further clinical studies to assess its efficacy in preventing hypoxaemia in high-risk newborns [26]).

A higher incidence of CA was observed in neonates classified as Small for Gestational Age (SGA), attributing this phenomenon to neurological alterations associated with intrauterine growth restriction (IUGR) [27]. These findings highlight how prenatal factors influence respiratory stability after birth and the likelihood of developing SDB [27]. Progress in diagnostic tools has been driven by Fukumizu (2004) and Foo et al. (2005, 2008), who confirmed that PTT reliably detects central breathing disruptions in children non-invasively [28–30]. Their work marks significant progress in bridging research and clinical practice, offering practical methods to monitor how breathing and brain activity interact during sleep without disturbing natural sleep patterns

Table 2. Summary of studies on central sleep-disordered breathing and sleep physiology in children.

Author(s) (year of publication)	Design	Subjects	Methods	Results	Conclusions	Relationship between SDB/OSA and Neurology
INFANTS						
Takashima S. and Becker (1986) [25]	Observational study	26 individuals, fetuses (gestational age 18 to 42 weeks), newborn (from 0 to 11 months)	Neurons in the medulla oblongata Golgi impregnation methods	Increase in pre-birth dendritic spines, decrease post-birth	Maturation of respiratory neurons occurs in prenatal and postnatal stages	Development of central respiratory control influenced by dendritic changes, implications for SIDS and apnea of prematurity
Schlaefke M.E. (1987) [26]	Experimental study	30 patients, aged 6 to 78	Paired stimuli (light, O ₂ /CO ₂), transcutaneous pO ₂ monitoring	Effective prevention of sleep hypoxemia in unventilated Infants	Potential preventive/therapeutic approach for central respiratory failure and sleep apnea	Direct intervention on central respiratory control mechanisms can modify neurological

						response s
Curzi-Dascalova L. (1996) [27]	Observational study	57 infants (31 AGA, 26 SGA)	Postnatal polygraphic records	SGA infants show more central breathing pauses than AGA	Respiratory control in infants Impaired SGA, possible brainstem changes	Neurological changes from IUGR affect central respiratory control
CHILDREN						
Fukumizu and Kohyama (2004) [28]	Clinical trial	19 healthy children (3 months - 7 years, mean 28 months)	PSG, respiratory plethysmography	Correlation between sighs, body movements, and central breathing pauses	Age- and status-related changes in breathing pauses	CSAs related to central sleep disorders
Foo JY (2005) [29]	Experimental study	5 infants (mean age 7.8 months)	PSG; PTT analysis	Sensitive PTT to detect central respiratory events	PTT as a non-invasive method of monitoring CA	Detection of central respiratory events in newborns
Foo JY et al. (2008) [30]	Observational study	28 children (age 6.2 ± 3.6 years)	PTT analysis during CSA and tidal breathing	Differences in PTT oscillations between CSA and normal breathing; PTT increase during clustered CSA	Predictive models for characteristics of respiratory events	Changes in vascular dynamics during sleep events reflect neurological and respiratory control alterations

Legend: AGA, appropriate for gestational age; AHI, apnea-hypopnea index; CA, central apnea; CSA, central sleep apnea; IUGR, intrauterine growth restriction, OAHs, obstructive sleep apnea-hypopnea syndrome; PSG,

polysomnography; PTT, pulse transit time; RP, respiratory polygraphy; SDB, sleep-disordered breathing; SGA, small for gestational age; SIDS, sudden infants death syndrome.

Table 3 shows the effects of SDB, particularly sleep apnoea, on central respiratory control and its interactions with the nervous and cardiovascular systems, with special attention to the paediatric implications of the studies summarised in Table 2.

The crucial role of dendritic spine development in the respiratory centres of the medulla oblongata has been highlighted, linking neuronal maturation to respiratory control in neonates. This study provides valuable insights into the mechanisms underlying primary apnoea in preterm infants and sleep apnoea associated with sudden infant death syndrome (SIDS), reinforcing the importance of neurodevelopmental monitoring in high-risk neonates [25].

An innovative method to prevent low oxygen levels in newborns was proposed, involving sensory interventions like light exposure and adjustments to breathing gases, paired with precise tracking of oxygen and carbon dioxide levels. Though promising, more clinical trials are needed to verify its usefulness in newborn care [26].

Infants born SGA showed more frequent breathing pauses, likely due to immature respiratory centres associated with growth restriction during pregnancy. This research stresses the importance of specialised respiratory monitoring for these high-risk infants [27].

The connection between central breathing irregularities (like pauses and sighs) and the brain's control of respiration has been explored, revealing that breathing regulation shifts with age and sleep phases. These insights reinforce that respiratory control evolves dynamically as the nervous system matures [28].

Finally, studies by Foo et al. validated the use of plethysmography and PTT as non-invasive tools for studying CSA. Their work has helped clarify the interactions between respiratory variability, oxygenation, and arterial stiffness, contributing to improved research methodologies for SDB in paediatric populations [29] [30].

Table 3. Literature review on sleep-disordered breathing and its impact on central respiratory control.

Author(s) (year of publication)	Type of apneas	Apnea Assessment Methods	Impact on Respiratory Centers and CNS	Evaluation of Respiratory Centers and CNS	Clinical Implications	Conclusions
INFANTS						
Takashi ma and Becker (1986) [25]	Primary apnea in prematurity, SIDS	Evaluation of neuronal development	Development of dendritic spines related to maturation of respiratory control	Examination of the density and maturation of dendritic spines	Potential use of neuronal development models as biomarkers or therapeutic targets	Neuronal development in the medulla oblongata crucial for respiratory control; important for research and preventiv

						e interventi ons
Schlaefk e ME (1987) [26]	CSA, Ondine syndrom e	Therapy with paired stimuli, transcutaneo us pO2 monitoring and end-tidal pCO2	Therapy stimulates respirator y responses , preventin g hypoxemi a	Monitoring of pO ₂ and pCO ₂ levels, PSG	Therapeu tic and preventiv e potential for SIDS and CSA	Efficacy of targeted therapeut ic stimulatio n in improvin g condition s of central respirator y insufficie ncy
Curzi- Dascalov a L. (1996) [27]	Apnea in infants SGA	Not specified	Increased breathing pauses and apnea index indicate impairme nt of respirator y centers	Compariso n of periodic breathing patterns and developme ntal parameters	Importan ce of monitorin g and supportin g respirator y functions in SGA infants	Complex interplay between delayed growth, respirator y control and CNS developm ent
CHILDR EN						
Fukumiz u and Kohyam a (2004) [28]	Sleep apnea, OSA	Observation of central pauses, sighs and gross movements during sleep	Central respirator y events related to neurologi cal controls of breathing, influence d by age and sleep stage	Analysis of patterns of respiratory events and their correlation with neurologic al developme nt	Need to understa nd age- and sleep stage- related changes to manage respirator y disorders	Importan ce of targeted therapeut ic strategies based on sleep developm ent and behavior
Foo JY et al. [30] [29]	CSA	Respiratory Inductance Plethysmogra	Decreased variability and	PTT analysis during	Reduced breathing effort and	Importan ce of targeted

		phy, PTT Analysis	command during episodes of apnea, indicating less active neurologi- cal control	normal breathing cycles and CSA	alteration s in oxygen saturatio- n during apnea can comprom- ise tissue oxygenati- on	treatment strategies to improve respirator- y regulatio- n and pattient outcomes
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Legend: CNS, central nervous system; CSA, central sleep apnea; OSA, obstructive sleep apnea; PTT, pulse transit time; PSG, polysomnography; SGA, smaal gestational age; SIDS, sudden infant death syndrome.

The evidence in Table 4 shows how SDB affects the brain's control of breathing in children with genetic syndromes, exploring how genes, body structures, and bodily functions contribute to these challenges.

In children with Prader-Willi syndrome, sleep studies by Schlüter et al. (1997) found that the main issue lies in how the brain regulates breathing, likely due to faulty brain signals and physical blockages in the airways [31]. Similarly, research comparing children with Down syndrome to others revealed that CSA is more common in this group, possibly tied to impaired brainstem function [32]. These findings illustrate how genetic risks and physical problems interact to worsen SDB.

A study on children with Pierre Robin sequence [33] observed uncoordinated breathing muscle activity during sleep, even when the brainstem appeared normal. This suggests that respiratory issues in some syndromes may stem from glitches in how specific brain networks operate rather than visible structural damage [33].

These patterns mirror what doctors see in children with brainstem injuries — whether present at birth or occurring later — where breathing pauses and shallow breathing are common. Such insights stress the importance of specialised care and close breathing monitoring in these vulnerable groups.

Table 4. Impact of Sleep-Disordered Breathing on Central Respiratory Control in Children with Genetic Syndromes.

Author(s) (year of publication)	Aims	Subjects	Methods	Results and conclusions	Relazione tra SDB/OSA e Neurologia
Schlüter B et al. (1997) [31]	Respiratory Control in Prader- Willi Syndrome	8 patients (6 weeks- 12.5 years)	Comparative study with PSG	Primary central respiratory control disorder in Prader- Willi Syndrome, aggravated by obesity	It shows a direct relationship between central respiratory dysfunction and the presence of SDB in Prader- Willi Syndrome

Ferri R et al. (1997) [32]	Breathing patterns during sleep in Down Syndrome	10 subjects subjects (8.6-32.2 years)	Comparative study	Higher prevalence of CSA in Down syndrome, suggesting brainstem dysfunction	Links CSA to central respiratory control dysfunctions in brainstem Down syndrome
Renault F et al. (2000) [33]	Neurophysiological investigations of the brainstem in the Pierre Robin Sequence	25 newborns (age not available)	Observational study with PSG and EMG	Functional disturbances in motor organisation affect breathing, but the absence of structural damage to the brainstem	Despite the absence of structural damage, functional motor control disorders contribute to SDB

Legend: CSA, central sleep apnea; EMG, electromyography; PSG, polysomnography; SDB, sleep-disordered breathing.

4. Discussion

Existing evidence suggests that even brief bouts of hypoxia – such as those encountered at high altitudes – can significantly worsen SDB indices (for instance, the AHI), increase sleep fragmentation, and place a heavier strain on the cardiovascular system in pediatric patients [20]. However, in adults, OSA acquires CSA as chemoreceptor sensitivity increases and central respiratory motor output instability occurs during a sojourn at high altitudes [34]. These findings point to the possibility that hypobaric hypoxia may disrupt respiratory control mechanisms at the level of the brainstem.

Studies in children using advanced measurement techniques (including TOI and PTT) also indicate that both CSA and OSA can lower cerebral oxygenation and activate the sympathetic nervous system, demonstrating that central events – often considered less severe – can trigger notable autonomic and cardiovascular responses [19,29,30].

Furthermore, breathing regulation in infancy and childhood involves substantial maturational and structural components [26] [27] [28–30]. Histopathological data highlight the critical role of dendritic development in the bulbar centres. At the same time, prenatal factors (such as IUGR, leading to SGA status) appear to increase the likelihood of respiratory irregularities in paediatric age [25] [27]. Finally, children with specific genetic syndromes – such as Prader–Willi [31], Down [35], or Pierre Robin sequence [33] – have been shown to experience dysfunctional central respiratory control stemming from both structural and functional abnormalities.

However, the heterogeneity of the included studies, such as small sample sizes [20] [29,31,32] and varying methodologies (PSG, transcutaneous pO₂ monitoring, plethysmography, PTT analysis) limits the generalizability of the results. Additionally, the scarcity of neuroimaging data in most studies precludes a direct correlation between physiological markers and brainstem alterations.

The exacerbation of SDB at high altitudes [20] underscores the sensitivity of paediatric respiratory centres to hypobaric hypoxia. Observed increases in the AHI, sleep fragmentation, and cardiovascular stress in this context suggest that hypoxia compromises the function of medullary

chemoreceptors in experimental data [36] [37] and the integration of autonomic feedback at the pons in models [38] and mammals [39], both crucial for maintaining rhythmic breathing [40]. This cohort's absence of overt neurocognitive deficits could reflect transient adaptive plasticity, such as increased serotonergic signalling in the brainstem in the mouse model [41] and temporarily stabilising respiratory drive in models [18]. However, prolonged or recurrent exposure to hypoxia could overwhelm compensatory capabilities in adults [42] and using animal models [43] in line with evidence suggesting that intermittent hypoxia induces oxidative stress in brainstem neurons [44], impairing synaptic plasticity over time [45].

While OSA is often seen as a problem of blocked airways, the issue goes beyond anatomy. The nervous system's ability to maintain steady airflow is equally essential [46]. For instance, the brainstem's emergency wake-up reaction—triggered by low oxygen—interrupts healthy sleep patterns [47], creating a harmful cycle of oxygen drops and abrupt awakenings [39] [2]. Over time, these repeated disruptions may gradually alter brain structure, shrinking grey matter in critical regions like the prefrontal cortex, hippocampus, and cerebellum, which could affect thinking, behaviour and learning [48] [13].

During non-REM sleep, CSA reduces brain oxygen levels like OSA [49], questioning the traditional focus on fixing airway mechanics alone in children [19]. This hints that flaws in brain networks governing breathing rhythms and arousal—specifically in the pons and medulla—might explain OSA and CSA [50] [51]. Post-mortem studies support this idea, showing that brainstem damage directly disrupts breathing control [52], while brain scans reveal weaker connections between the pons and prefrontal cortex in people with CSA [53]).

The dynamic development of medullary respiratory nuclei indicates a critical phase in childhood where the formation of dendritic spines is essential for establishing stable respiratory control [25]. Disruptions in this process, such as those caused by IUGR [27], can predispose infants to CSA, highlighting the long-term impact of prenatal insults on respiratory stability [54]. Similarly, the efficacy of sensory stimulation in reducing hypoxemia [26] suggests that immature brainstem circuits in infants can be externally modulated [55] [56]. However, the clinical translation of these techniques requires further validation.

In children with Prader-Willi syndrome, two mechanisms underlie SDB [31]: mechanical obstruction of the airways and reduced CO₂ sensitivity in medullary chemoreceptors. This duality mirrors observations in the Pierre Robin sequence [33], where functional disorganisation of pontomedullary networks, rather than overt structural anomalies, has been identified as the cause of respiratory dysfunction. These studies demonstrate that SDB arises from a complex interaction between brainstem dysfunctions and anatomical vulnerabilities in genetic syndromes [57]. In adult patients (aged 47.8±12.3 years) with genetic abnormalities, the instabilities in the ventilatory control system can generate temporary arrest of the respiratory drive (CSA), which is also a consequence of the obstruction of the airway [17]

In paediatric age, it has been observed that PTT and TOI [28–30] reflect the integration between autonomic responses and CNS involvement in SDB. A reduction in PTT during apnoea indicates sympathetic activation [58], while changes in TOI highlight alterations in oxygen distribution, both processes mediated by brainstem nuclei. The combined use of these tools and home PSG in children [20] allows for assessing SDB severity and central involvement in real-world contexts, bridging the gap between laboratory research and clinical practice.

Current evidence supports the hypothesis that intermittent hypoxia in children with OSA may contribute to damage to the brainstem respiratory centre through oxidative stress [59], inflammation [60] [61], and apoptosis, leading to compromised ventilatory control. Chronic intermittent hypoxia promotes a pro-oxidative state that destabilises rhythmogenesis in the preBötzinger complex, leading to sporadic failures in transmission to the XII nerve. These effects could perpetuate apneas and respiratory instability [62]. However, causality is often inferred from animal models [63–65], where the roles of oxidative stress and apoptosis-related neural injury are confirmed [66]. Therefore, OSA

worsens neurological outcomes in mice and increases neuronal death by enhancing neural apoptosis and neuroinflammation [67].

This comprehensive body of evidence—spanning pathophysiology, neurophysiological parameters, and clinical observations—clearly shows how intermittent hypoxia and SDB can disrupt the normal functioning of the brainstem's respiratory centres (medulla oblongata and pons). Children can be especially vulnerable, with these alterations often manifesting during sleep.

Repeated episodes of low oxygen (or intermittent hypoxia) can directly damage the brainstem regions responsible for controlling breathing and lead to broader health issues that weaken the body's ability to regulate respiration. Over time, these disturbances may disrupt sleep and waking hours, making it harder to maintain steady breathing patterns.

Identifying and treating the root causes of intermittent hypoxia is essential to safeguard the development and function of these critical breathing control areas in children.

5. Conclusions

Research shows that even short periods of low oxygen—like those occurring at high altitudes—can worsen markers of SDB, disrupt sleep quality, and put extra stress on the heart and blood vessels. These effects may weaken the brainstem's ability to regulate breathing. Both types of breathing pauses (central and obstructive) reduce oxygen flow to the brain and spark overactive "fight-or-flight" nervous system responses, with children particularly vulnerable. Given the limitations of existing studies in children, future research—using tools like advanced brain imaging—is crucial to fully grasp these issues' lasting impacts and create better prevention and treatment plans.

6. Patents

Author Contributions: Conceptualisation, M.Z. and A.P.; methodology, L.N.; software, M.Z.; validation, G.F., E.R. and S.G.; formal analysis, M.Z.; investigation, M.Z.; data curation, A.P. and G.P.; writing—original draft preparation, M.Z.; writing—review and editing, G.F., E.R., S.G.; visualisation, G.P.; supervision, G.P. and A.P. All authors have read and agreed to the published version of the manuscript.

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