HHS Public Access

Author manuscript

Anesth Analg. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Anesth Analg. 2021 July 01; 133(1): 93–103. doi:10.1213/ANE.0000000000005273.

Intermittent hypoxia and effects on early learning/memory: exploring the hippocampal cellular effects of pediatric OSA

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Abstract

This review provides an update on the neurocognitive phenotype of pediatric obstructive sleep apnea (OSA). Pediatric OSA is associated with neurocognitive deficits involving memory, learning, and executive functioning. Adenotonsillectomy (AT) is presently accepted as the first line surgical treatment for pediatric OSA, but the executive function deficits do not resolve post-

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surgery, and the timeline for recovery remains unknown. This finding suggests that pediatric OSA potentially causes irreversible damage to multiple areas of the brain. The focus of this review is the hippocampus, one of the 2 major sites of postnatal neurogenesis, where new neurons are formed and integrated into existing circuitry and the mammalian center of learning/memory functions. Here, we review the clinical phenotype of pediatric OSA, and then discuss existing studies of OSA on different cell types in the hippocampus during critical periods of development. This will set the stage for future study using preclinical models to understand the pathogenesis of persistent neurocognitive dysfunction in pediatric OSA.

Keywords

Hippocampus; Intermittent Hypoxia; Learning and Memory; Neurocognition; Pediatric Obstructive Sleep Apnea; Reactive Oxygen Species

Introduction

Obstructive sleep apnea (OSA) is characterized by repeated episodes of partial or complete airway obstruction, circadian dysrhythmias, and sleep fragmentation. Several types of neurocognitive deficits have been described based on the child's age and disease severity [1,2]. The pathogenesis of these changes, as well as why the neurocognitive changes in the pediatric population remain persistent despite treatment is a fundamental gap in our understanding of pediatric OSA [3,4]. We briefly describe the neurocognitive phenotype followed the effect of intermittent hypoxia on individual cell types in the hippocampus.

Methods

We searched PubMed and Cochrane databases for English language studies with the following keywords: Pediatric OSA, intermittent hypoxia, hippocampus, neural progenitors, ANPs, neural stem cells (NSCs), immature and mature neurons published from 2010-2020 along with relevant references within those articles. Emphasis was given to randomized clinical trials, and original controlled research studies along with articles/journals that are frequently studied by clinicians and scientists.

Overview of OSA

OSA is characterized by cyclical hypoxia/normoxia that induces reactive oxygen species (ROS) and oxidative stress [5]. Intermittent hypoxemia causes arousal from REM sleep with hypoxic hypercapnia being the most potent stimulus[6]. Sleep becomes fragmented, leading to daytime somnolence. Furthermore, the blood brain barrier (BBB), gray matter volume, and cerebral blood flow (CBF) are altered. The BBB becomes more permeable, gray matter volumes are decreased, and CBF fluctuates leading to a number of pathogenic changes [7] (Figure 1). Systemic inflammation[8] and sympathetic excitation [9] are additional hallmark features.

While direct data in pediatric OSA is lacking, changes in the BBB during periods of chronic inflammation have been implicated in sleep and neurodegenerative disorders in the adult population[10]. There are several contrasts between pediatric and adult OSA with regards to

the CNS features of the disease including symptomatology and areas of brain involved (Table 1).

Hypercarbia

Arterial PCO_2 rises during the apneic/hypopneic episodes in adult OSA[19]. Unfortunately, CO_2 levels are often not measured or are not reported in many studies on pediatric OSA[20]. From sparse data available, higher baseline PCO_2 levels in pediatric OSA correlated with persistent OSA following adenotonsillectomy [21]. But even with very severe pediatric OSA, the elevation in CO_2 is small and remains there for short periods of time in the context of total sleep time[21]. Therefore, we focus on chronic intermittent hypoxia rather than the hypercarbia, which in the context of current data appears to attenuate or has no effect on the nature of CNS injury.

Clinical Neurocognitive Phenotype of Pediatric OSA

Numerous studies in the pediatric OSA population have focused specifically on the CNS. Most of these studies are on school-aged children (5 years or older) with SDB/mild OSA[22–24]. Although changes secondary to OSA have been described in several areas of the brain, the hippocampal changes are the focus of this paper as it is the mammalian center of memory, learning, and early emotional behavior.[25] Any changes early in the process of rapid neuronal growth have significant effects later in life[26], partially explaining why even mild OSA in children can manifest with learning or cognitive deficits. Also, significant clinical deficits take time to come to the attention of parents or teachers as learning and memory integration is an ongoing process, [27]. What mediates ongoing learning and memory deficits post-AT remains unclear[28], and a preclinical model of the disease is urgently required. Given that early learning and memory are hippocampally mediated in the young[29], the remainder of this article will focus on pre-clinical studies in the hippocampus, specifically the effects of hypoxia on the various cell types.

Adult disease affects several key brain areas through both local mechanisms and effect on vasculature. The effect of these factors on brain areas in the pediatric population remain unknown, however there are changes in sleep spindles. Neurocognitive morbidity is seen in both populations. For example, with dementia, as seen in the adult population, there is improvement in cognitive metrics after CPAP therapy. In children however, there are not notable increases in learning memory function after intervention.

Hippocampus

The hippocampus is one of two neurogenic niches for postnatal mammalian neurogenesis [30], a dynamic throughout the lifespan [31] and has numerous functions including the generation of new memories, learning, and pattern separation which are a function of newborn neurons [32]. The neural stem cells (NSCs) reside in the sub granular zone (SGZ) of the dentate gyrus and give rise to amplifying neural progenitors (ANPs), which rapidly divide and eventually give rise to neuroblasts. Neuroblasts demonstrate high rates of apoptosis [33] and those that survive differentiate into immature neurons and subsequently mature neurons, which integrate into the hippocampal circuitry [34] (Figure 2).

They influence both regional physiology and the functional connectivity of the hippocampus with more distant brain regions, such as the prefrontal cortex, amygdala, and other structures within the limbic system.[35] Pattern separation, which is a critical function of the hippocampus, facilitates temporal event discrimination, spatial processing, and short-term memory storage [36].

The role of Reactive oxygen species

Reactive Oxygen Species (ROS) are generated during oxidative metabolism in mitochondria and consist of, amongst others, hydrogen peroxide, radical and non-radical oxygen species. Excess ROS formation, which occurs in OSA[37], leads to oxidative stress damage(Figure 3).

ROS have a dual role in that they are vital to cell repair and longevity [38], via both effects on transcription and synaptic activity. ROS effect transcription of several key gene mediators leading to several local and systemic effects. Acute intermittent hypoxia also does not lead to neuroinflammation [39]. However, continuous exposure is detrimental to CA-1 neurons in the hippocampus, which are selectively vulnerable to hypoxia in adult rodent models of OSA[40]. CA-1 neurons show delayed injury pattern with impaired cellular metabolism[41], from mitochondrial dysfunction[42] as well as endoplasmic reticulum (ER) stress[43,44].

Preclinical Rodent Models of Adult OSA

There have been two model types described for adult OSA. The first is the intermittent hypoxia model. This model demonstrated that after intermittent cyclical hypoxia for 14 days, adult rats demonstrated deficits in the Morris Water Maze Task (MWM)[40]. This test interrogates spatial memory which is a hippocampal function, and postmortem studies demonstrated CA-1 deficits. Follow up studies have revealed abnormalities in dentate gyrus (DG) function as well[45]. This exact model was replicated in younger rats[46], utilizing a moderate-severe clinical phenotype, which are not the children in whom neurobehavioral deficits are typically seen. The second model is the tracheal balloon occlusion model, which utilizes a surgically implanted tracheal balloon with intermittent inflation[47]. This model results in hypoxia and hypercarbia as seen in OSA. The latter model has not been neurobehaviorally validated. To date, there is no preclinical model recapitulating the neurocognitive phenotype of pediatric OSA. This has at least partially been due to a lack of validated learning and memory paradigms in neonatal mice. For example, MWM is not technically feasible due to hypothermia risk, and object recognition is not validated for use in this age group[48]. Accordingly, to enable further study of pediatric OSA, an age-appropriate animal model is necessary.

Oxygen tension in the rodent neonatal hippocampus

Hippocampal O_2 levels are far lower than the alveolar oxygen levels of 21% (room air/ normoxia) [49] however remain exquisitely vulnerable to hypoxic injury [50]. In the hippocampus normoxia is 8%, mild hypoxia is 5-8%, moderate hypoxia is oxygen at 1-5%, and less than 1% is severe hypoxia. Pimonidazole HCl labelling of hypoxic cells demonstrated that much of the SGZ lies within hypoxic zones which is believed to be less than 20 mm Hg[51]. Relative hypoxia in vitro (<5%) drives proliferation of neural progenitor and precursor cells[51,52] (Figure 4).

However, once these cells migrate away from hypoxic zones usually due to differentiation they seem to lose the hypoxic “protections” and are more susceptible to apoptosis [53–55]. All the studies were performed using continuous hypoxic conditions; the effects of intermittent hypoxia on early stem cell growth remains unknown. These findings demonstrate that oxygen balance within the dentate gyrus is tightly regulated and a small change in either direction has a profound effect on NSC behavior [56]. This balance is at least partially mediated by uncoupling protein 2(UP2), which effected mitochondrial-ER connections in the rodent cortex and hippocampus[57], as well as by nitric oxide(NO) for perivascular cells[58].

HIF-α is central to the cellular response to hypoxia[59]. HIF-α protects against hypoxic insult and allows for injury attenuation[60]. HIF-α inactivation causes impaired neurogenesis and learning deficits[61] even in the absence of hypoxia. Under hypoxic conditions, HIF-α promotes NSC proliferation[62]. This is through HIF-α effect on numerous mechanisms/ canonical pathways including p53, Notch, Wnt/beta-catenin, and Oct4 [63–67].

Hypoxic Effect on Neural Progenitors

Santilli et al. [68]demonstrated that severe hypoxia encouraged early ANP production from NSCs as compared to normoxic conditions. The same study showed that continuous in-vitro mild hypoxia drives self-renewal of NSCs. Similarly, deFillipis [69] demonstrated in vitro that mild hypoxia encouraged ANP production from NSCs whereas severe hypoxia facilitated apoptosis and quiescence. Chronic continuous hypoxia facilitates the survival and proliferation of progenitor cells [49]. In Notch knockout mice, the survival effect is not present, demonstrating that Notch1, at least in part, may mediate progenitor survival [85]. Furthermore, although hypoxic preconditioning increases differentiation of NSCs[70] , the presence of co-existing hypertension had no added effect on the differentiation [71], suggesting that change in CBF/small vessel disease contributes minimally to the behavior of NSCs. Even perivascular placement, with greater access to blood supply did not seem to confer any survival advantage[65].

ANPs have a precipitous drop in population after an acute hypoxic ischemic insult [72]. However, self-renewal begins after a brief dip in the progenitor pool [73]. Chronic severe hypoxia, however, appears to produce the opposite effect, decreasing the pool of ANPs, which in turn decreases the number of neuroblasts and immature/mature neurons as a downstream effect [74].

Intermittent hypoxia leads to an increase in progenitors; however, with a lower number of newborn neurons compared to normoxia in adult murine OSA models [45]. *Intermittent hypobaric hypoxia* also increases the number of progenitors and newborn neurons in the adult rodent hippocampus [75], again suggesting that changes in oxygen tension and baricity (pressure) within a small range can cause large shifts in the progenitor pool. Given the sensitivity of the progenitor pool to minor O2 tension differences, work is required on the effect of IH on the progenitor pool in the young.

Hypoxic Effect on Neuroblasts

Neuroblasts are exquisitely vulnerable to hypoxic injury[76]. It has been demonstrated that immature but committed neuroblasts die after an acute hypoxic insult, followed by

proliferation of ANPs that eventually replace the lost neuroblast pool [76] Because progenitors divide rapidly, a fast turnover of the neuroblasts can rescue the damage from the hypoxic injury [77]. Therefore, despite the sensitivity of certain neuroblast populations to hypoxic injury, there are multiple mechanisms by which this population is able to repopulate[78].

Hypoxic Effect on Immature Neurons

The mechanisms of injury and death of immature neurons is age-dependent and changes from apoptosis in young mammals to necrosis in older mammals [79]. Both GABA and glycine have been noted to be critical mediators [80], as well as Notch[81]. Neuronal death can be attenuated with iron chelators and free radical scavengers [82], suggesting that ROSs are involved [83]. The window of maximal damage is in postnatal days 2-5 in mice (corresponding to birth to 6 months age window in humans) [8485]. Mild hypothermia has been demonstrated to be somewhat protective after intermittent hypoxia at this stage [86].

Hypoxic Effect on Mature Neurons

Chatzi et al [53] used adult mice to test for the effects of hypoxia on newborn neurons. They demonstrated that these cells vacillate between continuous low-oxygen-tension environments, which promote early precursor proliferation, and continuous higher-oxygen-tension environments, which may be deleterious for newborn neurons. Taken together, these data suggest that oxygen tension is a critical component of newborn neuron fate and that the balance between hypoxia and normoxia is carefully maintained for newborn neurons [68,81] Given that integration into the hippocampal circuit is a competitive process, and not all newborn neurons are guaranteed survival benefit[87], oxygen tension being a key mediator of survival. This further suggests that any disruption in oxygen tension may have effects not only on the neuronal differentiation process, but also their ability to contribute to hippocampal circuitry and function.

CA-3 neurons are more resistant to hypoxia vs CA-1 neurons, postulated to be due to Ca^{+2} mediation, [40] although the mechanisms are multifactorial[41]. Multiple mechanisms of hippocampal neuronal alterations have been suggested including c-AMP-protein kinase A signaling and CREB-mediated gene transcription [80]. Furthermore, glutamate mediates CA-1 neuronal apoptosis to hypoxia in guinea pig apnea models [88]. Magnetic resonance spectroscopy (MRS) has also demonstrated that N-acetyl-aspartate (NAA, neuronal integrity biomarker) and choline (membrane turnover) were decreased in rodents exposed to intermittent hypoxia from P2-P12 [83**]**. This effect was validated in humans, where change in choline levels in the midbrain were correlated with an increased in excitotoxic biomarkers including glutamate[89]. Cofilin, an actin-binding protein which disassembles actin filaments, mediates dendritic spine loss and decreased hippocampal neuronal plasticity in CA-1 neurons [90]. Elevated cofilin activity from sleep deprivation is caused by cAMP-degrading phosphodiesterase-4A5 (PDE4A5), which hampers cAMP-PKA-LIMK signaling. Inhibition of cofilin activity prevented spine loss and increased plasticity. Overall, there is a clear decline in the number of mature neurons after hypoxic insult, depending on degree and duration of hypoxemia [91]. While adult OSA models have demonstrated disorganization of CA-1 neuron architecture after IH exposure[85], the pediatric neuronal changes remain unknown.

Hypoxic Effect on Glial Cells

Glial cells (astrocytes, oligodendrocytes, and microglia) have scavenging and neuroprotective functions. Astrocytes have been found to be relatively more resistant to hypoxia than are microglia, through multiple mechanisms [92].

Astrocytes

Intermittent hypoxia in rats produces hippocampal astrocytosis with a high rate of neuronal cell death; however, chronic hypoxia increases both neuronal survival and expression of S100β (secreted by astrocytes or by injured neurons) [93] as compared to acute hypoxia. NADPH oxidase(Nox), a mammalian enzyme involved in both astrocytic and microglial phagocytic burst [94], has been demonstrated to be putative to several processes including hypoxia/reoxygenation injury, carbonylation, and pro-inflammatory states[95]. NADPH has been demonstrated to be involved in the pathogenesis of the neurocognitive deficit seen in adult OSA [96]. A postulated mechanism is due to upregulation of CHOP (CCAAT enhancer binding homologous protein), which mediates HIF-α, Nox 2, oxidative and apoptosis markers[97]. Hypoxia also stimulates astrocyte expression of aquaporin 4 (AQ4), which leads to local edema [98]. Aquaporin 1 is also increased in areas of high content of astrocytes, suggesting that cytotoxic edema is central to pathogenesis in OSA [99].

At least a part of astrocytes' initial tolerance to hypoxia is conferred by upregulation of glucose transport and uptake in both astrocytes and mature neurons [100], postulated to be due to osmotic and electrochemical gradients[101] and altered transport of other ions such as Na+ and neurotransmitters including glutamate across the cell junctions[102]. However, altering RAGE (**r**eceptor for **a**dvanced **g**lycosylation **e**nd products) and nuclear factor kappa b (NF-kB), which are involved in converting astrocytes into a pro-inflammatory phenotype, reduced the neurocognitive deficit in adult male mice [103]. Taken together, these suggest that astrocytic function is central to continued neuronal survival and health in OSA.

Oligodendrocytes

Oligodendrocytes myelinate axons and are found only in the CNS. After intermittent hypoxic exposure in neonatal rats, pathological findings include decreased oligodendrocyte markers [104]. Several myelin proteins (MBP, PLP, MAG, and CNPase) were also down-regulated after exposure to intermittent hypoxia, suggesting arrest of oligodendrocyte maturation [105]. Oligodendrocytes have also been demonstrated to be a key player in memory consolidation in mammals[106]. Therefore, any arrest or injury would not only affect motor function, but memory as well.

Microglia

Microglia mediate central nervous system ROS through NADPH oxidase, mitochondria, and excitatory neurotransmitters [107]. Given the neurocognitive damage from OSA is at least partially mediated through ROS, there is a yet to be elucidated role for microglia in the pathogenesis of OSA induced neurocognitive dysfunction. Since microglia are also involved in synaptic pruning, perturbations in microglial activity have been postulated in several psychiatric disorders[108]. Suppression of microglia activation after sleep deprivation has been

demonstrated to lead to improvement in adult neurogenesis and spatial memory[109].The implication is that microglial activation is a key player in sleep deprivation based neurocognitive dysfunction.

Furthermore, TLR4, MAPK, transcription factors, and epigenetic factors all have been suggested to contribute to microglial activation [110]. In animal models, the injection of LPS in stressed rats, but not unstressed rats, activate the pro-inflammatory microglial phenotype, leading directly to cell injury [111]. This finding suggests that the interplay of oxidative stress and other environmental factors including ROS may be central to the pathogenesis of neurocognitive change, especially in the young [112]. In summary, glial cells play critical roles in the post-hypoxic neuronal injury models; however, much remains to be elucidated about their function, especially in the pediatric population.

Conclusion:

Intermittent hypoxia in the young may have long lasting neurocognitive effects. These changes, while affecting multiple areas of the brain, are more pronounced in the hippocampus, which is the mammalian center for early learning and memory. These changes can be attributed to several constitutive changes in hippocampal cell types and function. Given the connections between the hippocampus and other areas of the brain, the changes can be more widespread. While the clinical reversibility of these changes is unknown, there is an urgent need for a preclinical model to further study this common disorder of childhood.

Acknowledgments

Financial Disclosures: Financial Disclosures: AC, ACA, and MT have no relevant financial disclosures. FK is supported by R01ES029442, I01CX0000104, and R01AI135803. RSR is supported by R01HL130249 and R21OD025327. SR is supported by R21EY027447 and R21EY028690. No other relevant non-financial disclosures.

Abbreviations:

ANP	(amplified nuclear progenitors)
AT	(adenotonsillectomy)
BBB	(blood brain barrier)
CBF	(cerebral blood flow)
CIHH	(chronic intermittent hypoxia and hypercarbia)
CNS	(central nervous system)
OSA	(obstructive sleep Apnea)
ROS	(reactive oxygen species)
SES	(socioeconomic status)
REM	(rapid eye movement)
NREM	(non-rapid eye movement)

SGZ	(sub granular zone)
NSC	(neural stem cells)

References

1. Kheirandish L, Gozal D. Neurocognitive dysfunction in children with sleep disorders. Dev Sci 2006;9:388–99. [PubMed: 16764612]
2. Galland BC, Dawes PJ, Tripp EG, Taylor BJ. Changes in behavior and attentional capacity after adenotonsillectomy. Pediatr Res 2006;59:711–6. [PubMed: 16627887]
3. Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, Mitchell RB, Amin R, Katz ES, Arens R, Paruthi S, Muzumdar H, Gozal D, Thomas NH, Ware J, Beebe D, Snyder K, Elden L, Sprecher RC, Willging P, Jones D, Bent JP, Hoban T, Chervin RD, Ellenberg SS, Redline S, Childhood Adenotonsillectomy T. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med 2013;368:2366–76. [PubMed: 23692173]
4. Biggs SN, Vlahandonis A, Anderson V, Bourke R, Nixon GM, Davey MJ, Horne RS. Long-term changes in neurocognition and behavior following treatment of sleep disordered breathing in school-aged children. Sleep 2014;37:77–84. [PubMed: 24470698]
5. Lavie L Obstructive sleep apnoea syndrome--an oxidative stress disorder. Sleep Med Rev 2003;7:35–51. [PubMed: 12586529]
6. Marcus CL, Lutz J, Carroll JL, Bamford O. Arousal and ventilatory responses during sleep in children with obstructive sleep apnea. J Appl Physiol (1985) 1998;84:1926–36. [PubMed: 9609786]
7. Macey PM, Henderson LA, Macey KE, Alger JR, Frysinger RC, Woo MA, Harper RK, Yan-Go FL, Harper RM. Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 2002;166:1382–7. [PubMed: 12421746]
8. Punjabi NM, Beamer BA. C-reactive protein is associated with sleep disordered breathing independent of adiposity. Sleep 2007;30:29–34. [PubMed: 17310862]
9. Li T, Chen Y, Gua C, Wu B. Elevated Oxidative Stress and Inflammation in Hypothalamic Paraventricular Nucleus Are Associated With Sympathetic Excitation and Hypertension in Rats Exposed to Chronic Intermittent Hypoxia. Front Physiol 2018;9:840. [PubMed: 30026701]
10. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun 2017;60:1–12. [PubMed: 26995317]
11. Dalmases M, Sole-Padulles C, Torres M, Embid C, Nunez MD, Martinez-Garcia MA, Farre R, Bargallo N, Bartres-Faz D, Montserrat JM. Effect of CPAP on Cognition, Brain Function, and Structure Among Elderly Patients With OSA: A Randomized Pilot Study. Chest 2015;148:1214–23. [PubMed: 26065720]
12. Li HJ, Dai XJ, Gong HH, Nie X, Zhang W, Peng DC. Aberrant spontaneous low-frequency brain activity in male patients with severe obstructive sleep apnea revealed by resting-state functional MRI. Neuropsychiatr Dis Treat 2015;11:207–14. [PubMed: 25653530]
13. Torelli F, Moscufo N, Garreffa G, Placidi F, Romigi A, Zannino S, Bozzali M, Fasano F, Giulietti G, Djonlagic I, Malhotra A, Marciani MG, Guttmann CR. Cognitive profile and brain morphological changes in obstructive sleep apnea. Neuroimage 2011;54:787–93. [PubMed: 20888921]
14. Halbower AC, Degaonkar M, Barker PB, Earley CJ, Marcus CL, Smith PL, Prahme MC, Mahone EM. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med 2006;3:e301. [PubMed: 16933960]
15. Kerner NA, Roose SP. Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms. Am J Geriatr Psychiatry 2016;24:496–508. [PubMed: 27139243]
16. Lin WC, Huang CC, Chen HL, Chou KH, Chen PC, Tsai NW, Chen MH, Friedman M, Lin HC, Lu CH. Longitudinal brain structural alterations and systemic inflammation in obstructive sleep apnea before and after surgical treatment. J Transl Med 2016;14:139. [PubMed: 27188598]

17. Brockmann PE, Damiani F, Pincheira E, Daiber F, Ruiz S, Aboitiz F, Ferri R, Bruni O. Sleep spindle activity in children with obstructive sleep apnea as a marker of neurocognitive performance: A pilot study. Eur J Paediatr Neurol 2018;22:434–9. [PubMed: 29477593]
18. Waters KA, Chawla J, Harris MA, Heussler H, Black RJ, Cheng AT, Lushington K. Cognition After Early Tonsillectomy for Mild OSA. Pediatrics 2020;145.
19. Earing C, Owen J, Griffith-Mcgeever C, McKeon D, Engeli S, Moore J, Kubis HP. An act of balance: interaction of central and peripheral chemosensitivity with inflammatory and anti-inflammatory factors in obstructive sleep apnoea. Respir Physiol Neurobiol 2019.
20. Socarras MA, Landau BP, Durr ML. Diagnostic techniques and surgical outcomes for persistent pediatric obstructive sleep apnea after adenotonsillectomy: A systematic review and meta-analysis. Int J Pediatr Otorhinolaryngol 2019;121:179–87. [PubMed: 30925395]
21. Isaiah A, Hamdan H, Johnson RF, Naqvi K, Mitchell RB. Very Severe Obstructive Sleep Apnea in Children: Outcomes of Adenotonsillectomy and Risk Factors for Persistence. Otolaryngol Head Neck Surg 2017;157:128–34. [PubMed: 28397574]
22. Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of Sleep-disordered Breathing Severity on Cognitive Performance Measures in a Large Community Cohort of Young School-aged Children. Am J Respir Crit Care Med 2016;194:739–47. [PubMed: 26930303]
23. Smith DL, Gozal D, Hunter SJ, Philby MF, Kaylegian J, Kheirandish-Gozal L. Impact of sleep disordered breathing on behaviour among elementary school-aged children: a cross-sectional analysis of a large community-based sample. Eur Respir J 2016;48:1631–9. [PubMed: 27587553]
24. Mietchen JJ, Bennett DP, Huff T, Hedges DW, Gale SD. Executive Function in Pediatric Sleep-Disordered Breathing: A Meta-analysis. J Int Neuropsychol Soc 2016;22:839–50. [PubMed: 27481012]
25. McEwen BS. Early life influences on life-long patterns of behavior and health. Ment Retard Dev Disabil Res Rev 2003;9:149–54. [PubMed: 12953293]
26. Takada SH, Motta-Teixeira LC, Machado-Nils AV, Lee VY, Sampaio CA, Polli RS, Malheiros JM, Takase LF, Kihara AH, Covolan L, Xavier GF, Nogueira MI. Impact of neonatal anoxia on adult rat hippocampal volume, neurogenesis and behavior. Behav Brain Res 2016;296:331–8. [PubMed: 26416672]
27. Hollands C, Tobin MK, Hsu M, Musaraca K, Yu TS, Mishra R, Kernie SG, Lazarov O. Depletion of adult neurogenesis exacerbates cognitive deficits in Alzheimer's disease by compromising hippocampal inhibition. Mol Neurodegener 2017;12:64. [PubMed: 28886753]
28. Song SA, Tolisano AM, Cable BB, Camacho M. Neurocognitive outcomes after pediatric adenotonsillectomy for obstructive sleep apnea: A systematic review and meta-analysis. Int J Pediatr Otorhinolaryngol 2016;83:205–10. [PubMed: 26968078]
29. Johnson EG, Prabhakar J, Mooney LN, Ghetti S. Neuroimaging the sleeping brain: Insight on memory functioning in infants and toddlers. Infant Behav Dev 2020;58:101427.
30. Taupin P Adult neural stem cells, neurogenic niches, and cellular therapy. Stem Cell Rev 2006;2:213–9. [PubMed: 17625257]
31. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. Nat Med 1998;4:1313–7. [PubMed: 9809557]
32. Kempermann G Why new neurons? Possible functions for adult hippocampal neurogenesis. J Neurosci 2002;22:635–8. [PubMed: 11826092]
33. Li B, Sierra A, Deudero JJ, Semerci F, Laitman A, Kimmel M, Maletic-Savatic M. Multitype Bellman-Harris branching model provides biological predictors of early stages of adult hippocampal neurogenesis. BMC Syst Biol 2017;11:90. [PubMed: 28984196]
34. Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH. Synapse formation on neurons born in the adult hippocampus. Nat Neurosci 2007;10:727–34. [PubMed: 17486101]
35. Ramirez-Amaya V, Marrone DF, Gage FH, Worley PF, Barnes CA. Integration of new neurons into functional neural networks. J Neurosci 2006;26:12237–41. [PubMed: 17122048]
36. Kesner RP. A behavioral analysis of dentate gyrus function. Prog Brain Res 2007;163:567–76. [PubMed: 17765738]

37. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. Chest 2015;147:266–74. [PubMed: 25560865]
38. Lavie L Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. Sleep Med Rev 2015;20:27–45. [PubMed: 25155182]
39. Peters ME, Kimyon RS, Mitchell GS, Watters JJ. Repetitive acute intermittent hypoxia does not promote generalized inflammatory gene expression in the rat CNS. Respir Physiol Neurobiol 2015;218:1–10. [PubMed: 26213117]
40. Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. J Neurosci 2001;21:2442–50. [PubMed: 11264318]
41. Bartsch T, Dohring J, Reuter S, Finke C, Rohr A, Brauer H, Deuschl G, Jansen O. Selective neuronal vulnerability of human hippocampal CA1 neurons: lesion evolution, temporal course, and pattern of hippocampal damage in diffusion-weighted MR imaging. J Cereb Blood Flow Metab 2015;35:1836–45. [PubMed: 26082014]
42. Medvedeva YV, Ji SG, Yin HZ, Weiss JH. Differential Vulnerability of CA1 versus CA3 Pyramidal Neurons After Ischemia: Possible Relationship to Sources of Zn2+ Accumulation and Its Entry into and Prolonged Effects on Mitochondria. J Neurosci 2017;37:726–37. [PubMed: 28100752]
43. Xu LH, Xie H, Shi ZH, Du LD, Wing YK, Li AM, Ke Y, Yung WH. Critical Role of Endoplasmic Reticulum Stress in Chronic Intermittent Hypoxia-Induced Deficits in Synaptic Plasticity and Long-Term Memory. Antioxid Redox Signal 2015;23:695–710. [PubMed: 25843188]
44. Chandrakantan A, Adler AC. Pediatric Obstructive Sleep Apnea: Neurocognitive Consequences. Curr Anesthesiol Rep 2019;9:110–5.
45. Khuu MA, Pagan CM, Nallamothu T, Hevner RF, Hodge RD, Ramirez JM, Garcia AJ 3rd. Intermittent Hypoxia Disrupts Adult Neurogenesis and Synaptic Plasticity in the Dentate Gyrus. J Neurosci 2019;39:1320–31. [PubMed: 30587544]
46. Row BW, Kheirandish L, Neville JJ, Gozal D. Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. Pediatr Res 2002;52:449–53. [PubMed: 12193683]
47. Crossland RF, Durgan DJ, Lloyd EE, Phillips SC, Reddy AK, Marrelli SP, Bryan RM, Jr. A new rodent model for obstructive sleep apnea: effects on ATP-mediated dilations in cerebral arteries. Am J Physiol Regul Integr Comp Physiol 2013;305:R334–42. [PubMed: 23761641]
48. Contreras MP, Born J, Inostroza M. The expression of allocentric object-place recognition memory during development. Behav Brain Res 2019;372:112013. [PubMed: 31173799]
49. Schneider J, Berndt N, Papageorgiou IE, Maurer J, Bulik S, Both M, Draguhn A, Holzhutter HG, Kann O. Local oxygen homeostasis during various neuronal network activity states in the mouse hippocampus. J Cereb Blood Flow Metab 2017:271678X17740091.
50. Schmidt-Kastner R Genomic approach to selective vulnerability of the hippocampus in brain ischemia-hypoxia. Neuroscience 2015;309:259–79. [PubMed: 26383255]
51. Erecinska M, Silver IA. Tissue oxygen tension and brain sensitivity to hypoxia. Respir Physiol 2001;128:263–76. [PubMed: 11718758]
52. Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 2010;7:483–95. [PubMed: 20887954]
53. Chatzi C, Schnell E, Westbrook GL. Localized hypoxia within the subgranular zone determines the early survival of newborn hippocampal granule cells. Elife 2015;4:e08722. [PubMed: 26476335]
54. Platero-Luengo A, Gonzalez-Granero S, Duran R, Diaz-Castro B, Piruat JI, Garcia-Verdugo JM, Pardal R, Lopez-Barneo J. An O2-sensitive glomus cell-stem cell synapse induces carotid body growth in chronic hypoxia. Cell 2014;156:291–303. [PubMed: 24439383]
55. Suda T, Takubo K, Semenza GL. Metabolic regulation of hematopoietic stem cells in the hypoxic niche. Cell Stem Cell 2011;9:298–310. [PubMed: 21982230]
56. Vieira HL, Alves PM, Vercelli A. Modulation of neuronal stem cell differentiation by hypoxia and reactive oxygen species. Prog Neurobiol 2011;93:444–55. [PubMed: 21251953]

57. Varela L, Schwartz ML, Horvath TL. Mitochondria controlled by UCP2 determine hypoxia-induced synaptic remodeling in the cortex and hippocampus. Neurobiol Dis 2016;90:68–74. [PubMed: 26777666]
58. Lourenco CF, Santos RM, Barbosa RM, Cadenas E, Radi R, Laranjinha J. Neurovascular coupling in hippocampus is mediated via diffusion by neuronal-derived nitric oxide. Free Radic Biol Med 2014;73:421–9. [PubMed: 24887095]
59. Ashok BS, Ajith TA, Sivanesan S. Hypoxia-inducible factors as neuroprotective agent in Alzheimer's disease. Clin Exp Pharmacol Physiol 2017;44:327–34. [PubMed: 28004401]
60. Xing J, Lu J. HIF-1alpha Activation Attenuates IL-6 and TNF-alpha Pathways in Hippocampus of Rats Following Transient Global Ischemia. Cell Physiol Biochem 2016;39:511–20. [PubMed: 27383646]
61. Carrica L, Li L, Newville J, Kenton J, Gustus K, Brigman J, Cunningham LA. Genetic inactivation of hypoxia inducible factor 1-alpha (HIF-1alpha) in adult hippocampal progenitors impairs neurogenesis and pattern discrimination learning. Neurobiol Learn Mem 2019;157:79–85. [PubMed: 30521851]
62. Qi C, Zhang J, Chen X, Wan J, Wang J, Zhang P, Liu Y. Hypoxia stimulates neural stem cell proliferation by increasing HIF1alpha expression and activating Wnt/beta-catenin signaling. Cell Mol Biol (Noisy-le-grand) 2017;63:12–9.
63. Chavali PL, Saini RK, Matsumoto Y, Agren H, Funa K. Nuclear orphan receptor TLX induces Oct-3/4 for the survival and maintenance of adult hippocampal progenitors upon hypoxia. J Biol Chem 2011;286:9393–404. [PubMed: 21135096]
64. Cui XP, Xing Y, Chen JM, Dong SW, Ying DJ, Yew DT. Wnt/beta-catenin is involved in the proliferation of hippocampal neural stem cells induced by hypoxia. Ir J Med Sci 2011;180:387–93. [PubMed: 20811817]
65. Mazumdar J, O'Brien WT, Johnson RS, LaManna JC, Chavez JC, Klein PS, Simon MC. O2 regulates stem cells through Wnt/beta-catenin signalling. Nat Cell Biol 2010;12:1007–13. [PubMed: 20852629]
66. Pistollato F, Rampazzo E, Persano L, Abbadi S, Frasson C, Denaro L, D'Avella D, Panchision DM, Della Puppa A, Scienza R, Basso G. Interaction of hypoxia-inducible factor-1alpha and Notch signaling regulates medulloblastoma precursor proliferation and fate. Stem Cells 2010;28:1918–29. [PubMed: 20827750]
67. Simon MC, Keith B. The role of oxygen availability in embryonic development and stem cell function. Nat Rev Mol Cell Biol 2008;9:285–96. [PubMed: 18285802]
68. Santilli G, Lamorte G, Carlessi L, Ferrari D, Rota Nodari L, Binda E, Delia D, Vescovi AL, De Filippis L. Mild hypoxia enhances proliferation and multipotency of human neural stem cells. PLoS One 2010;5:e8575. [PubMed: 20052410]
69. De Filippis L, Delia D. Hypoxia in the regulation of neural stem cells. Cell Mol Life Sci 2011;68:2831–44. [PubMed: 21584807]
70. Motomura A, Shimizu M, Kato A, Motomura K, Yamamichi A, Koyama H, Ohka F, Nishikawa T, Nishimura Y, Hara M, Fukuda T, Bando Y, Nishimura T, Wakabayashi T, Natsume A. Remote ischemic preconditioning protects human neural stem cells from oxidative stress. Apoptosis 2017;22:1353–61. [PubMed: 28951984]
71. Pedroso D, Nunes AR, Diogo LN, Oudot C, Monteiro EC, Brenner C, Vieira HLA. Hippocampal neurogenesis response: What can we expect from two different models of hypertension? Brain Res 2016;1646:199–206. [PubMed: 27235865]
72. Lim DC, Brady DC, Po P, Chuang LP, Marcondes L, Kim EY, Keenan BT, Guo X, Maislin G, Galante RJ, Pack AI. Simulating obstructive sleep apnea patients' oxygenation characteristics into a mouse model of cyclical intermittent hypoxia. J Appl Physiol (1985) 2015;118:544–57. [PubMed: 25429097]
73. Daval JL, Pourie G, Grojean S, Lievre V, Strazielle C, Blaise S, Vert P. Neonatal hypoxia triggers transient apoptosis followed by neurogenesis in the rat CA1 hippocampus. Pediatr Res 2004;55:561–7. [PubMed: 14739363]

74. Chung E, Kong X, Goldberg MP, Stowe AM, Raman L. Erythropoietin-mediated neuroprotection in a pediatric mouse model of chronic hypoxia. Neurosci Lett 2015;597:54–9. [PubMed: 25899777]

75. Zhu XH, Yan HC, Zhang J, Qu HD, Qiu XS, Chen L, Li SJ, Cao X, Bean JC, Chen LH, Qin XH, Liu JH, Bai XC, Mei L, Gao TM. Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats. J Neurosci 2010;30:12653–63. [PubMed: 20861371]

76. Miles DK, Kernie SG. Hypoxic-ischemic brain injury activates early hippocampal stem/progenitor cells to replace vulnerable neuroblasts. Hippocampus 2008;18:793–806. [PubMed: 18446826]

77. Felling RJ, Snyder MJ, Romanko MJ, Rothstein RP, Ziegler AN, Yang Z, Givogri MI, Bongarzone ER, Levison SW. Neural stem/progenitor cells participate in the regenerative response to perinatal hypoxia/ischemia. J Neurosci 2006;26:4359–69. [PubMed: 16624956]

78. Costine BA, Missios S, Taylor SR, McGuone D, Smith CM, Dodge CP, Harris BT, Duhaime AC. The subventricular zone in the immature piglet brain: anatomy and exodus of neuroblasts into white matter after traumatic brain injury. Dev Neurosci 2015;37:115–30. [PubMed: 25678047]

79. Liu CL, Siesjo BK, Hu BR. Pathogenesis of hippocampal neuronal death after hypoxia-ischemia changes during brain development. Neuroscience 2004;127:113–23. [PubMed: 15219674]

80. Zhao P, Qian H, Xia Y. GABA and glycine are protective to mature but toxic to immature rat cortical neurons under hypoxia. Eur J Neurosci 2005;22:289–300. [PubMed: 16045482]

81. Zhang K, Zhao T, Huang X, Wu LY, Wu K, Zhu LL, Fan M. Notch1 mediates postnatal neurogenesis in hippocampus enhanced by intermittent hypoxia. Neurobiol Dis 2014;64:66–78. [PubMed: 24368168]

82. Almli LM, Hamrick SE, Koshy AA, Tauber MG, Ferriero DM. Multiple pathways of neuroprotection against oxidative stress and excitotoxic injury in immature primary hippocampal neurons. Brain Res Dev Brain Res 2001;132:121–9. [PubMed: 11744116]

83. Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D. Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol 2006;575:807–19. [PubMed: 16825295]

84. Dutta S, Sengupta P. Men and mice: Relating their ages. Life Sci 2016;152:244–8. [PubMed: 26596563]

85. Gozal E, Row BW, Schurr A, Gozal D. Developmental differences in cortical and hippocampal vulnerability to intermittent hypoxia in the rat. Neurosci Lett 2001;305:197–201. [PubMed: 11403939]

86. Kwak M, Lim S, Kang E, Furmanski O, Song H, Ryu YK, Mintz CD. Effects of Neonatal Hypoxic-Ischemic Injury and Hypothermic Neuroprotection on Neural Progenitor Cells in the Mouse Hippocampus. Dev Neurosci 2015;37:428–39. [PubMed: 26087836]

87. Bergami M, Berninger B. A fight for survival: the challenges faced by a newborn neuron integrating in the adult hippocampus. Dev Neurobiol 2012;72:1016–31. [PubMed: 22488787]

88. Fung SJ, Xi MC, Zhang JH, Sampogna S, Yamuy J, Morales FR, Chase MH. Apnea promotes glutamate-induced excitotoxicity in hippocampal neurons. Brain Res 2007;1179:42–50. [PubMed: 17888415]

89. Macey PM, Sarma MK, Prasad JP, Ogren JA, Aysola R, Harper RM, Thomas MA. Obstructive sleep apnea is associated with altered midbrain chemical concentrations. Neuroscience 2017;363:76–86. [PubMed: 28893651]

90. Havekes R, Park AJ, Tudor JC, Luczak VG, Hansen RT, Ferri SL, Bruinenberg VM, Poplawski SG, Day JP, Aton SJ, Radwanska K, Meerlo P, Houslay MD, Baillie GS, Abel T. Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1. Elife 2016;5.

91. d'Anglemont de Tassigny X, Sirerol-Piquer MS, Gomez-Pinedo U, Pardal R, Bonilla S, Capilla-Gonzalez V, Lopez-Lopez I, De la Torre-Laviana FJ, Garcia-Verdugo JM, Lopez-Barneo J. Resistance of subventricular neural stem cells to chronic hypoxemia despite structural disorganization of the germinal center and impairment of neuronal and oligodendrocyte survival. Hypoxia (Auckl) 2015;3:15–33. [PubMed: 27774479]

92. Guo G, Bhat NR. Hypoxia/reoxygenation differentially modulates NF-kappaB activation and iNOS expression in astrocytes and microglia. Antioxid Redox Signal 2006;8:911–8. [PubMed: 16771681]

93. Aviles-Reyes RX, Angelo MF, Villarreal A, Rios H, Lazarowski A, Ramos AJ. Intermittent hypoxia during sleep induces reactive gliosis and limited neuronal death in rats: implications for sleep apnea. J Neurochem 2010;112:854–69. [PubMed: 20002528]

94. Quinn MT, Gauss KA. Structure and regulation of the neutrophil respiratory burst oxidase: comparison with nonphagocyte oxidases. J Leukoc Biol 2004;76:760–81. [PubMed: 15240752]

95. Zhan G, Serrano F, Fenik P, Hsu R, Kong L, Pratico D, Klann E, Veasey SC. NADPH oxidase mediates hypersomnolence and brain oxidative injury in a murine model of sleep apnea. Am J Respir Crit Care Med 2005;172:921–9. [PubMed: 15994465]

96. Nair D, Dayyat EA, Zhang SX, Wang Y, Gozal D. Intermittent hypoxia-induced cognitive deficits are mediated by NADPH oxidase activity in a murine model of sleep apnea. PLoS One 2011;6:e19847. [PubMed: 21625437]

97. Chou YT, Zhan G, Zhu Y, Fenik P, Panossian L, Li Y, Zhang J, Veasey S. C/EBP homologous binding protein (CHOP) underlies neural injury in sleep apnea model. Sleep 2013;36:481–92. [PubMed: 23564995]

98. Kaur C, Sivakumar V, Zhang Y, Ling EA. Hypoxia-induced astrocytic reaction and increased vascular permeability in the rat cerebellum. Glia 2006;54:826–39. [PubMed: 16977604]

99. Baronio D, Martinez D, Fiori CZ, Bambini-Junior V, Forgiarini LF, Pase da Rosa D, Kim LJ, Cerski MR. Altered aquaporins in the brains of mice submitted to intermittent hypoxia model of sleep apnea. Respir Physiol Neurobiol 2013;185:217–21. [PubMed: 23123204]

100. Yu S, Zhao T, Guo M, Fang H, Ma J, Ding A, Wang F, Chan P, Fan M. Hypoxic preconditioning up-regulates glucose transport activity and glucose transporter (GLUT1 and GLUT3) gene expression after acute anoxic exposure in the cultured rat hippocampal neurons and astrocytes. Brain Res 2008;1211:22–9. [PubMed: 18474279]

101. Rose CR, Waxman SG, Ransom BR. Effects of glucose deprivation, chemical hypoxia, and simulated ischemia on Na+ homeostasis in rat spinal cord astrocytes. J Neurosci 1998;18:3554–62. [PubMed: 9570787]

102. Orellana JA, Hernandez DE, Ezan P, Velarde V, Bennett MV, Giaume C, Saez JC. Hypoxia in high glucose followed by reoxygenation in normal glucose reduces the viability of cortical astrocytes through increased permeability of connexin 43 hemichannels. Glia 2010;58:329–43. [PubMed: 19705457]

103. Angelo MF, Aguirre A, Aviles Reyes RX, Villarreal A, Lukin J, Melendez M, Vanasco V, Barker P, Alvarez S, Epstein A, Jerusalinsky D, Ramos AJ. The proinflammatory RAGE/NF-kappaB pathway is involved in neuronal damage and reactive gliosis in a model of sleep apnea by intermittent hypoxia. PLoS One 2014;9:e107901. [PubMed: 25265561]

104. Simonova Z, Sterbova K, Brozek G, Komarek V, Sykova E. Postnatal hypobaric hypoxia in rats impairs water maze learning and the morphology of neurones and macroglia in cortex and hippocampus. Behav Brain Res 2003;141:195–205. [PubMed: 12742256]

105. Cai J, Tuong CM, Gozal D. A neonatal mouse model of intermittent hypoxia associated with features of apnea in premature infants. Respir Physiol Neurobiol 2011;178:210–7. [PubMed: 21699999]

106. Steadman PE, Xia F, Ahmed M, Mocle AJ, Penning ARA, Geraghty AC, Steenland HW, Monje M, Josselyn SA, Frankland PW. Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice. Neuron 2020;105:150–64 e6. [PubMed: 31753579]

107. Yang Q, Wang Y, Feng J, Cao J, Chen B. Intermittent hypoxia from obstructive sleep apnea may cause neuronal impairment and dysfunction in central nervous system: the potential roles played by microglia. Neuropsychiatr Dis Treat 2013;9:1077–86. [PubMed: 23950649]

108. Hanger B, Couch A, Rajendran L, Srivastava DP, Vernon AC. Emerging Developments in Human Induced Pluripotent Stem Cell-Derived Microglia: Implications for Modelling Psychiatric Disorders With a Neurodevelopmental Origin. Front Psychiatry 2020;11:789. [PubMed: 32848951]

109. Wadhwa M, Prabhakar A, Ray K, Roy K, Kumari P, Jha PK, Kishore K, Kumar S, Panjwani U. Inhibiting the microglia activation improves the spatial memory and adult neurogenesis in rat hippocampus during 48 h of sleep deprivation. J Neuroinflammation 2017;14:222. [PubMed: 29141671]

110. Kiernan EA, Smith SM, Mitchell GS, Watters JJ. Mechanisms of microglial activation in models of inflammation and hypoxia: Implications for chronic intermittent hypoxia. J Physiol 2016;594:1563–77. [PubMed: 26890698]

111. Espinosa-Oliva AM, de Pablos RM, Villaran RF, Arguelles S, Venero JL, Machado A, Cano J. Stress is critical for LPS-induced activation of microglia and damage in the rat hippocampus. Neurobiol Aging 2011;32:85–102. [PubMed: 19286276]

112. Daulatzai MA. Role of sensory stimulation in amelioration of obstructive sleep apnea. Sleep Disord 2011;2011:596879. [PubMed: 23470957]

113. Semenza GL, Prabhakar NR. The role of hypoxia-inducible factors in carotid body (patho) physiology. J Physiol 2018;596:2977–83. [PubMed: 29359806]

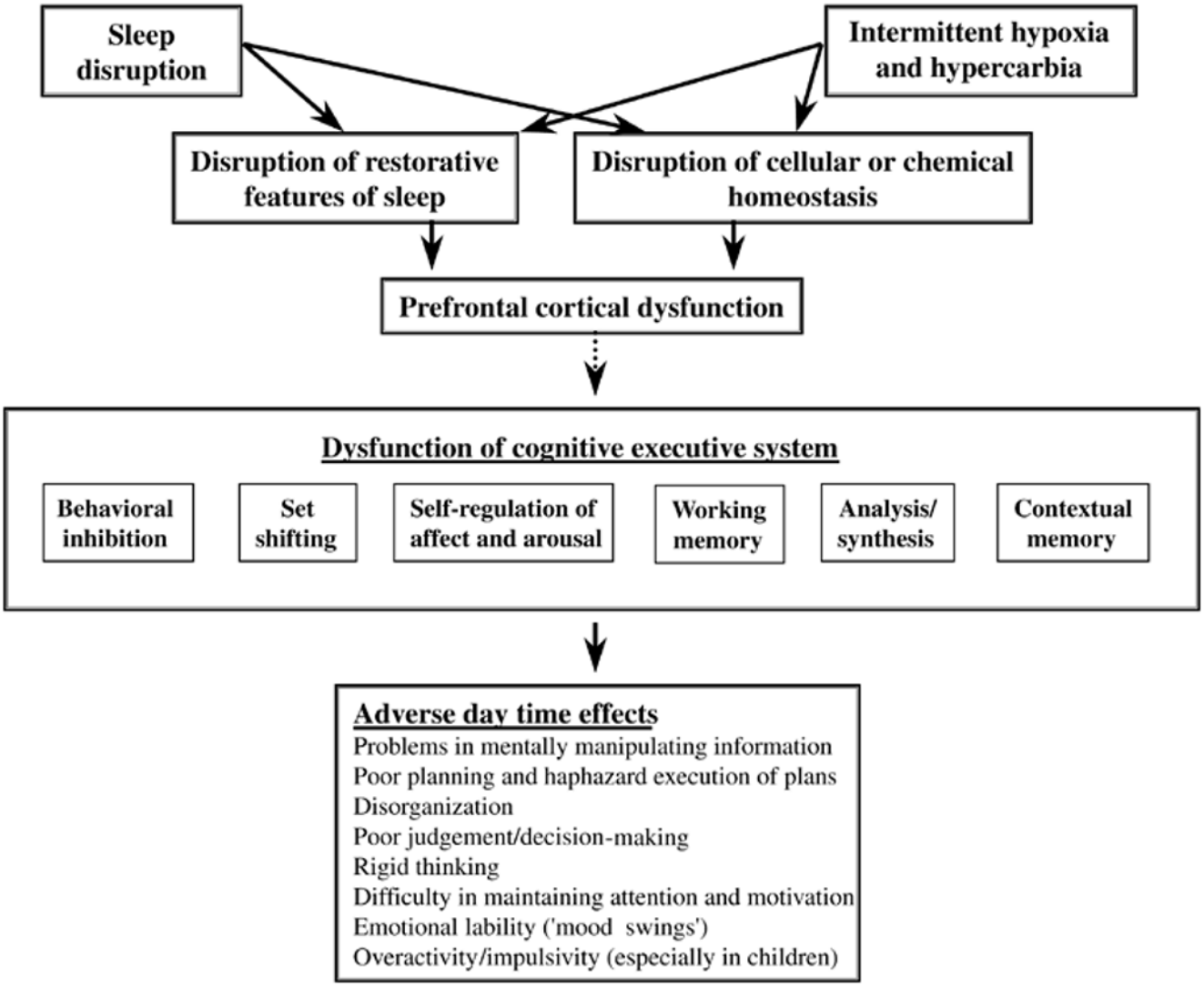

Figure 1:

Demonstrates the multifactorial effects of arousal and somnolence on memory and learning. There are multiple pathological mechanisms that are affected, leading to multipathway effects on several organ systems, including the CNS. These effects lead to a variety of clinical presentations. The classical adult presentation of OSA is with daytime somnolence, whereas in pediatric OSA a number of children present with problems in the school environment. Reproduced with permission from: Beebe DW, Gozal D. J Sleep Res 2002;11(1):1-16.

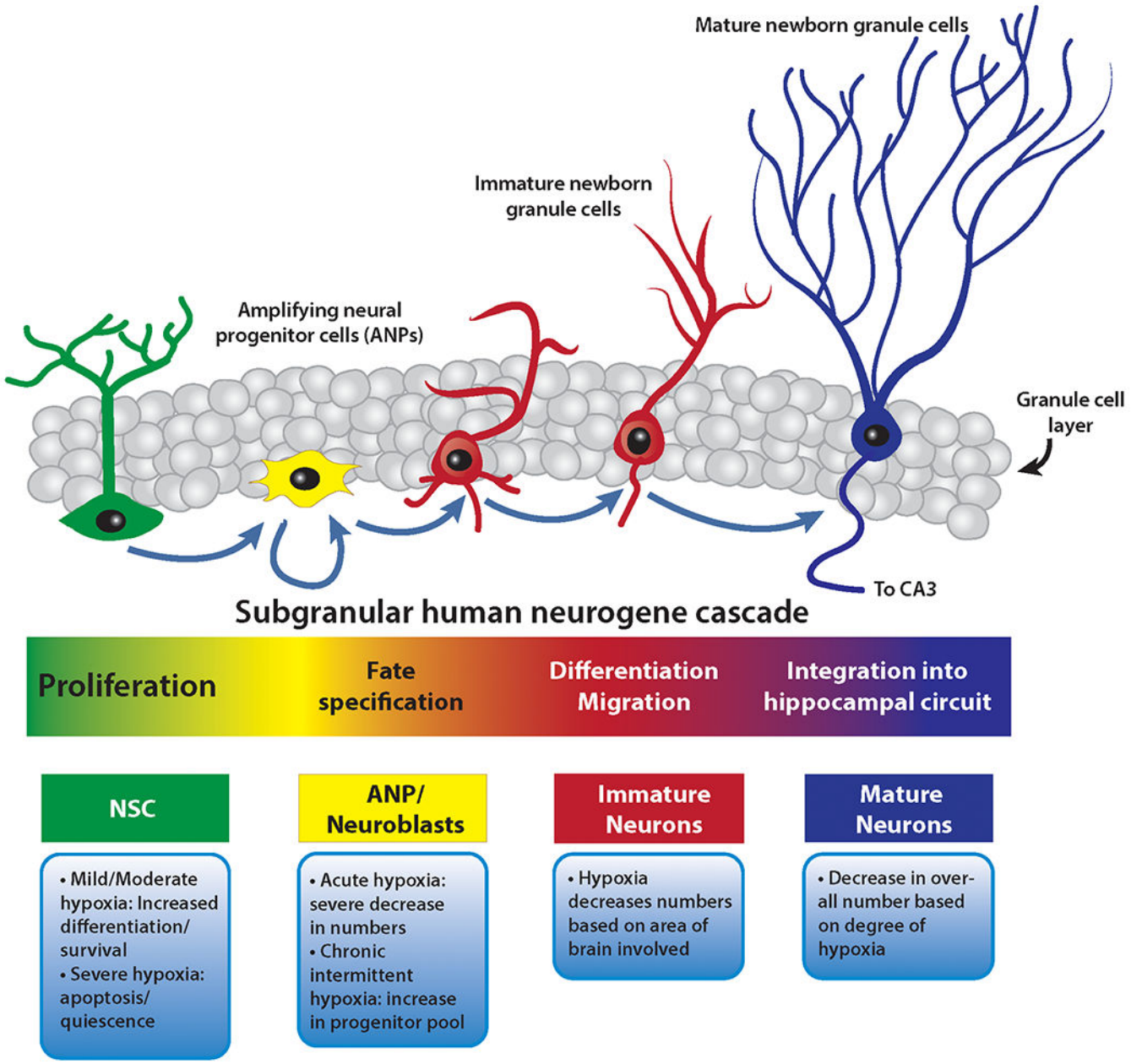

Figure 2:

Various cell types and the effect of hypoxia on these cell types in the mammalian hippocampus. Hypoxia has different effects at different parts of the neurogenic cascade, and promotes apoptosis beyond the NSC stage. The morphology of each cell type under intermittent hypoxia has not been studied.Therefore, while varying levels of hypoxia may effect different areas of the cascade differently, the effects of intermittent hypoxia, with consequent ROS formation has not been elucidated. There could be differences in number, morphology, and function, all of which need to interrogated to properly understand how the mammalian hippocampus responds to intermittent hypoxia.

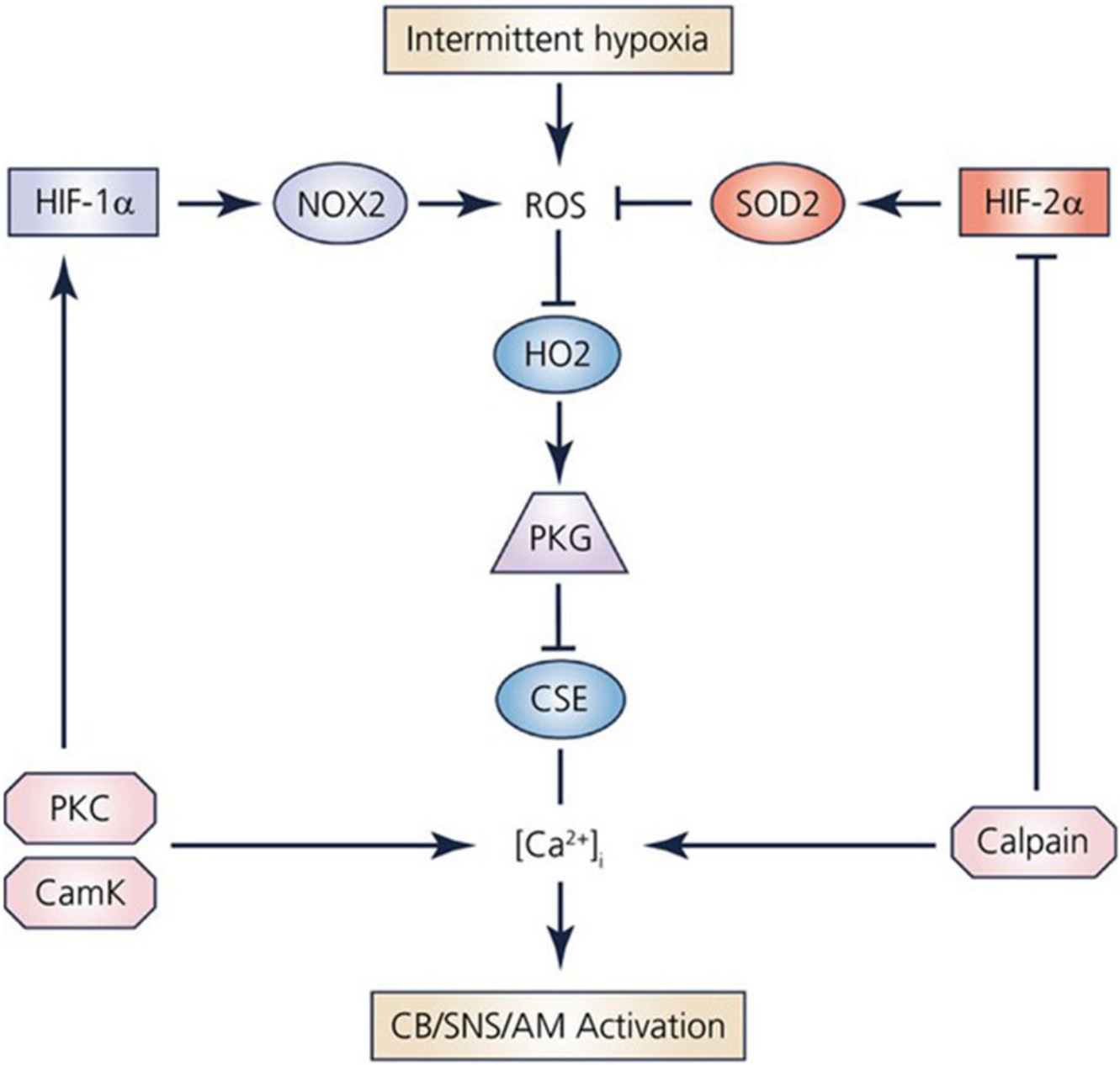

Figure 3:

The interplay between ROS, HIF-α, Superoxide dismutase (SOD), haemoxygenase 2(HO2), and pathophysiological changes including sympathetic nervous system activation. HIF-α has downstream effects on several other pathways as well. The effects of ROS in the context of the pediatric OSA, specifically with regards to the intermittent hypoxia stimulus, remain unknown. There is a convergence on the end-point of both SNS/adrenal medulla activation, which leads to a higher level of circulating catecholamines in these patients. This has been one of the postulated mechanisms of hypertension in both pediatric and adult OSA. AM: Adrenal Medulla, SNS: sympathetic nervous system, Nox2 (NAPDH oxidase 2), PKG: Protein Kinase G, PKC: Protein Kinase C. With permission[113]

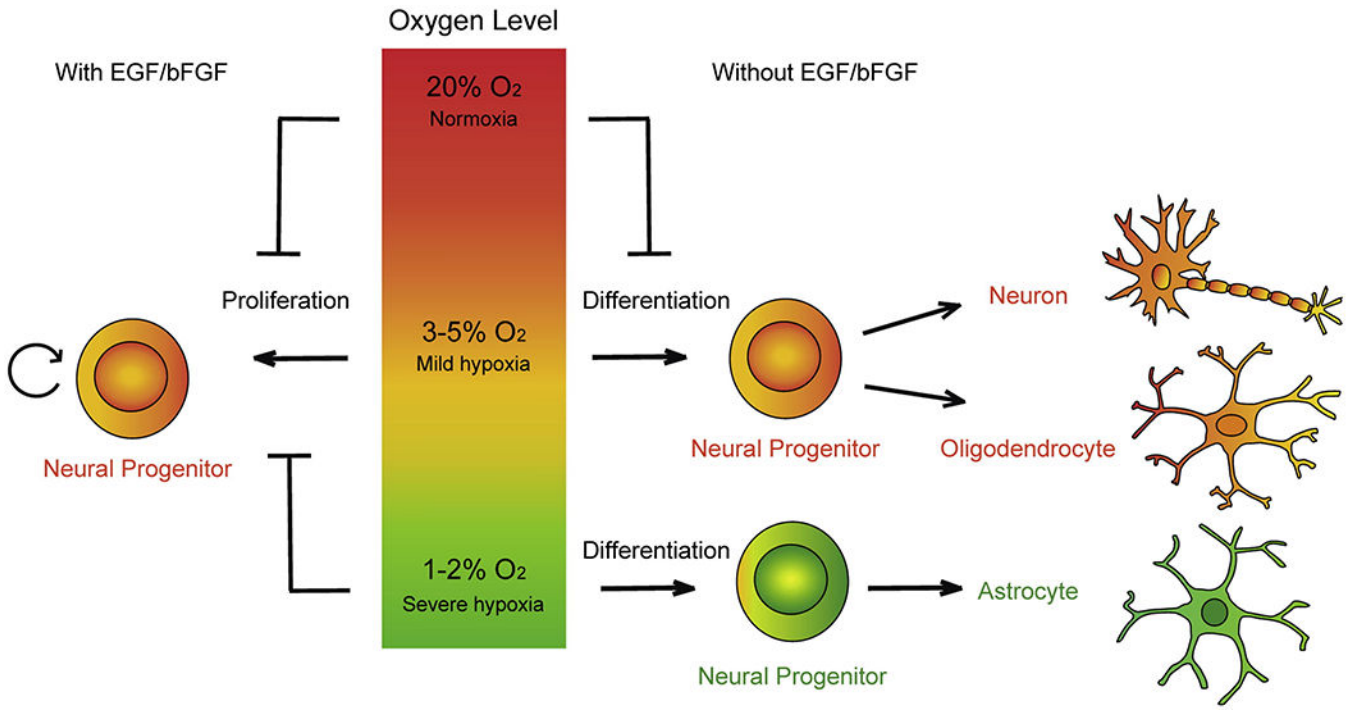

Figure 4:

The effects of various levels of hypoxia on progenitor cell behavior. Severe continuous hypoxia seems to facilitate astrocytic transformation, whereas moderate hypoxia promotes precocious differentiation.Since self-renewal is important in the maintenance of the stem cell pool, both forms of hypoxia cause depletion of the progenitor pool leading to a net loss of available NSCs. The long term effect of progenitor pool depletion on lifelong learning and memory is not well understood. Xie Y, Lowery W. Methods 2018 with permission.

Table 1:

Brain areas, postulated mechanisms, and reversibility of neurocognitive dysfunction.

	Adult	**Pediatric**
Areas of Brain involved	• Right Middle Frontal Lobe Gyrus[11] • Posterior cingulate gyrus • Left inferior frontal gyrus[12] • Bilateral hippocampi[13]	• Bilateral hippocampi, Right frontal cortex[14]
Pathogenesis of neurocognitive dysfunction	• Small vessel disease[15] • CBF changes • Systemic inflammation[16]	• Oxidative Stress • Sleep Spindle Changes [17]
Reversibility with therapy	• Improvement in most cognitive domains after CPAP	• Improvement in behavior after surgery, but persistence in executive function deficits[3,18]