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SEX DIFFERENCES IN NEONATAL ANOXIA:
A Behavioural and Histological Study in Wistar Rats.

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“Life is just a certain amount of time and energy.

Putting this time and energy to maximum use for everyone’s wellbeing is all that matters.”

— Sadhguru Jaggi

Resumo geral

A anoxia neonatal está associada a déficits no desenvolvimento neurológico. Exploramos a diferença de sexo na anoxia neonatal, pois os deficits neurologicos e cognitivos tem sido pouco abordados em relacao ao sexo apos anóxia neonatal.

Portanto, decidimos, avaliar os efeitos a curto e medio da asfixia perinatal em modelo animal adaptado e validado. Esse estímulo não invasivo e global, pela exposição de ratos neonatos (30 h) a 100% de nitrogênio, simula as condições clínicas de bebês prematuros humanos (cerca de 6 meses de gestação), que apresentam complicacoes pela falta de oxigenio de forma adequada. Foi utilizada bateria de testes para reflexos sensorio motores, labirinto aquático de Morris, estudos de labirinto em cruz elevado e alodinia mecânica. Assim como, avaliação de alteracoes histologicas em areas neurais relacionadas aos objetivos abordados foram tambem realizadas. Os resultados mostraram alterações nos ratos submetidos a anoxia neonatal nesses testes, sendo o macho mais vulnerável ao impacto negativo do estímulo , em relacao a fêmea. Os resultados demonstram que a anoxia neonatal afeta os reflexos sensoriomotores avaliados, de forma diferenciada em machos e femeas e que sao tambem idade-dependentes e com com decrescimo no numero de celulas nas areas avaliadas. Avaliacoes comportamentais identificaram que a anoxia causou comportamento semelhante a ansiedade, menor nos animais experimentais em relacao aos controles, sendo que as femeas menos ansiosas que os machos. O machos anoxia apresentaram deficit cognitivo na memória espacial em relacao femea e respectivos controles. Foi observado decrescimo celular em regioes do hipocampo (CA1, CA3, DG) dependentes do sexo. A anoxia neonatal diminuiu significativamente o limiar a nocicepcao mecanica (alodinia) associada a alteracoes no nucleo sensorio motor do talamo (VPL) e na substancia nigra compacta. Esses resultados são relevantes na interpretação dos eventos já observados nessa condição clinica mundial e ressaltam a importancia de considerar diferencas de sexo nas pesquisas, a fim de orientar a busca por abordagens e procedimentos terapeuticos efetivos.

General Abstract

Purpose/aim of the study: Neonatal anoxia is associated with neurodevelopmental deficits. We explored gender difference in neonatal anoxia. Only few studies have been reported describing neurological, cognitive and behavioral deficits following perinatal asphyxia along with sex difference. We therefore decided to study long term effects of perinatal asphyxia in a well- documented animal model resembling the clinical situation. This stimulus, induced by exposure of 30-hour old pups to 100% nitrogen, represents a non-invasive and global stimulus, which simulates clinical conditions of human pre-

term babies (around 6 gestational months). Examinations consisted of a battery of motor and reflex tests, Morris water maze, elevated plus maze and mechanical allodynia studies. Alteration in anoxia rats were seen in these tests and male being more vulnerable for detrimental effect of the stimulus than the female. Along with development and behavior alteration histological damage in vulnerable regions linked to above deficits were seen. The present data demonstrates that neonatal anoxia, besides determining only transitory defects in behavior, profoundly affects cognitive abilities and as seeing different field (CA1, CA3, DG) of hippocampus; Substantia Nigra Compact Dorsal, and Ventroposterolateral thalamus nucleus. These results might be of relevance in the interpretation of the substrate of the cognitive impairment seen clinically. This is still a health concern worldwide, a risk factor for several mental and neurological disorders showing a delayed clinical onset. Serial neurobehavioral follow-up is still executed on the premature infants who is absent of detectable abnormalities in early children.

I General Introduction

Neonatal anoxia

Neonatal anoxia, is a medical condition resulting from deprivation of oxygen during time of birth which can affect physically but in majority affects the brain. It is considered a global clinical problem, which leads to serious and lasting consequences of mental retardation, cerebral palsy, epilepsy, hearing and visual deficiencies, along with deficities in motor and behavioural development (Hedner and Lundborg, 1980; Volpe, 1992; Dell'Anna et al., 1993; Dell'Anna et al., 1995; Dell'Anna et al., 1997; Faraone and Biederman., 1998; Vannucci et al., 1999; Cannon et al., 2002; Wainwright et al., 2004; Caputa et al., 2005; Casolini et al., 2005; Mikati et al., 2005; Rogalska et al., 2006; Majeed et al., 2007; Chen et al., 2007).

It also triggers infant's mortality and lifelong disability that affects 0.1–0.3% of full-term infants and nearly 60% of low-weight premature infants (Kurinczuk et al., 2010). The incidence of neonatal anoxic insults appears to be 2–4/1000 full-term infants, but this rate is much higher (approximately 60%) in low-weight premature newborns, making it a public health concern (Vannucci et al., 1997; Laviola et al., 2004).

The severity of these brain injury appears to be sex dependent, affecting more the male neonates, resulting in more severe neurological outcomes and poor recovery as compared to females with similar brain injuries (Waddell et al., 2016; Huang et al., 2016). Previous research showed that neonatal anoxia affected somatic growth, ontogenesis of physical development and onset of neurological reflexes in comparison to control animals, with sex differences in physical and ontogenetic reflex parameters. Male anoxic rats were more vulnerable in histological analysis at adolescence (Kumar et al., 2017). It is established that young male and female rats present asymmetries in antioxidant system properties (Sanches et al., 2013) and different molecular mechanisms of cell death (Zhu et al., 2006). Such differences might possibly be the cause of altered behavioural and morphological responses as previously described (Bona et al., 1998).

The vulnerability of the brain to the lack of oxygen turns it into the most damaged structure, especially in the border areas of the cerebral arteries and in areas of the cerebral cortex, brain stem, subcortical oligodendrial region, periventricular region and basal nuclei (Courville et al., 1950; Volpe & Pasternak., 1977; Nakamura et al., 1986; Khong et al., 2003).

Some of the neurological complications resulting from this condition are: hypoxic-ischemic encephalopathy, delayed neuromotor development, cerebral palsy, periventricular leukomalacia, mental retardation, learning disability, memory impairment, epilepsy, hyperactivity, and other behavioral changes (Vannucci et al., 2000, Funayama et al., 2005, Majeed et al., 2007, Morozova & Belosouva, 2009; Back & Rosenberg, 2014). Research on Hippocampal vulnerability to oxygen deprivation using rodent models of both hypoxia–ischemia and hypoxia (Johnston, 2001; Daval and Vert, 2004; Liu et al., 2008; Yang et al., 2011); reported that the extension of the damage appears to be related to the hippocampal plasticity, due to its neurogenese ability (Shors et al., 1989), which might minimize deficits in spatial learning and memory (Buwalda et al., 1995; Cannon et al., 2002; Caputa et al., 2005; Rogalska et al., 2006; Winocur et al., 2006).

Although cognitive changes and cerebral cell death have been extensively investigated using other animal models of oxygen deprivation, the methodological approach employed in the present study provides advantages. First, it is non-invasive global oxygen deprivation in neonatal rats up to 30 h after birth appears to parallel the experience of low-weight premature infants because the rats are subjected to anoxia at a brain maturation stage that corresponds to that of humans born prematurely (Semple et al., 2013), thus representing an analogously valid model. Second, one of the main findings following oxygen deprivation at this period in rodent models corresponds to white matter damage associated with no gross morphological alterations in gray matter (Puyal et al., 2013).

In the other hand, the injury also decreases glucocorticoids levels, altering HPA, which increases corticosterone and alter monoaminergic systems functioning (Flandreu et al., 2012; Krishnan et al., 2008). Perinatal hypoxia ischemia has shown that locomotor disorders and reduced anxiety are associated with low level of

dopamine content in the rat brain and with simultaneous substantia nigra injury (Boksa et al., 20004).

Moreover, a common brain abnormality in individuals born at very preterm is the thinning of the corpus callosum (cc), particularly of the posterior body (splenium) (Stewart et al., 1999; Peterson et al., 2000). Such injury may be partly explained by its vulnerability to hypoxic–ischaemic damage and haemorrhage but, also because of the immature stage of oligodendrocytes (Back et al., 2001).

Oxygen deprivation in human neonates.

After hypoxia, some children may recover neurologically without sequelae, while others develop permanent deficits (Bennet et al., 2000). Hypoxia also represents a state of low oxygen content in the organic tissues that can occur due to several factors, such as obstruction Physics of blood flow at any level of the body circulation or even in an environment with low oxygen concentrations in the air. This exposure of the brain to the condition of low oxygen and reduced blood supply is called Ischemic Hypoxia (HI), whose consequences include cerebral palsy and behavioral abnormalities (Lynch et al., 2009). In humans, changes in perfusion and oxygenation of the brain is the main cause of perinatal brain damage (Nyakas et al., 1996). Approximately 0.3-0.9% of newborn humans are exposed to prolonged perinatal ischemia-anoxia or anoxic injury, a period in which they are particularly susceptible to tissue damage (Tutor et al., 1996). Ischemic Hypoxia (HI) in human neonates during gestational weeks 23-32 are considered premature, they usually present damage to the developing subcortical white matter due to cell death.

Injury due to HI occurs more frequently in the context of unequivocal clinical impairment, such as placental dysfunction or prolonged labor, or premature birth and cardiorespiratory resuscitation. This condition known as periventricular leukomalacia (PVL) appears to be associated with decreased blood and consequent hypotension. Obstetric complications may also be associated with schizophrenia (Boksa et al., 2004). However, hypoxemia and acidosis are causes of cerebral palsy that are related to abnormal development in childhood, which present limitations in learning and motor immobility (Volpe et al., 2002). In this condition, seizures and severe motor

damage also occur in children, and severe cases can result in death (Tuor et al., 2012).

Central Nervous System and Oxygen Deprivation

In oxygen deprivation a complex cascade of virtually simultaneous biochemical events is triggered which promotes interruption of energy metabolism, acid-base imbalance, accumulation of oxygen-reactive species and excitatory amino acids in the extracellular space, loss of cellular water balance and onset of apoptosis (Vexler et al., 2001). It is important to point out that these events are fast and short-lived, so the timeframe for therapeutic interventions is greatly reduced.

Neonatal damage in rats can disrupt the neuroendocrine system, present low levels of circulating glucocorticoids, altering the hypothalamic-pituitary-adrenal (HPA) axis and can cause abdominal obesity. Increased basal corticosterone levels increase pulse rate, and may result in hypertension. The resulting alterations may also affect the monoaminergic system in regions such as striatum, prefrontal cortex and hippocampus and cause depletion of serotonin, norepinephrine and dopamine. These conditions are associated with depressive symptoms (Flandreu et al., 2012; Krishnan et al., 2008).

Dopamine decreases as a function of decreased tyrosine hydroxylase activity in the motor cortex and hippocampus and may reduced anxiety in animal models (Perrin et al., 2004; Hoeger et al., 2000). In perinatal asphyxia, the literature reports. Furthermore, hypoglycemia results from this insult which has been reported in relation to the change in structure and remodeling of synapses and altered neural plasticity. Synaptic modifications related to the efficacy of neuronal transmission, such as those of long-term potential, are common in this condition (Jourdane et al., 2002).

The brain, because it is high metabolic tissue requires adequate supply of glucose and oxygen to maintain its normal functions. This critical requirement is compromised during biochemical changes generated by anoxic injury, leading to excitotoxicity and

influx of Ca2 + ions, resulting in overproduction of nitric oxide (NO), and other reactive oxygen species (ROS) within the mitochondria (Marschitz et al., 2014). The depletion of ATP by anoxia or hypoxia has important consequences, since it implies a failure in the functioning of sodium-potassium ionic pumps, activation of free radical formation (Dell'Anna et al., 1997), changes in the phosphorylation state of Different enzymes and structural proteins. Failure in ionic pumps causes ionic passage through the membrane below the concentration gradients and promotes consequent depolarization with lethal consequences and massive loss of neurotransmitters such as glutamate, aspartate and dopamine into the extracellular space in a toxic amount (Lofton et al. , 1989).

Stages of Brain Development in Rodents and Humans

The main event in the formation of CNS in all vertebrates is the formation of a specialized fold of ectodermal tissue called the neural tube, from which the spinal column and the brain subsequently differentiate. Neural tube formation occurs approximately midway through gestation in gestational day (GD) 10.5-11 and 9.95 in rats. In humans, this event occurs earlier during prenatal development, between GD 24 and 28 (3-4 weeks), in a gestational period of 266-280 days (40Weeks) (Rice et al., 2000).

Critical Period of Injury and Cell Proliferation

The critical period corresponds to the one in which there is greater susceptibility of the neurons and the glia to damages, this comprises the phase of the proliferation and cellular migration, which is considerable in the last trimester of gestation of the human brains and in rats occurs in the week post (Bayer et al., 1993). During development, in the neonatal mammalian brain, the layer of glutamatergic and gammaaminobutyric acid (GABA), or GABAergic neurons, between the immature cerebral cortex and the region of the white matter below the neural plate is the source of new neurons (Kostovic et al., 1989). The cortical neurogenesis in the rat begins in GD 9.5 and is completed around the PND (Rice et al., 2000) whereas in humans, there is predominance during gestation, which can continue until 2.5 years of age (Hovda et al., 2003).

In the second week of gestational development of rats and in the first month of gestation in humans, specific areas of the CNS begin to form with neurogenesis and cell migration in the brain, then follow the sequence of developmental processes that includes proliferation, migration, differentiation, onset of synapses, apoptosis and myelination. During the latter part of pregnancy and the first postnatal month, oligodendrocytes should develop their myelin sheath around axons. The maturation of axons and the appearance of synapses in humans occurs during the third trimester of the first year after birth (Mason et al., 1984).

Previous studies in neonatal anoxia, from this laboratory, have demonstrated the detrimental effects of this stimulus, both in glial and neural populations Of the hippocampus, depending on the region and its development period (Allemandi, 2011). In neuronal populations of the hippocampus (Amom's horn and dentate gyrus) a longitudinal effect of this stimulus was observed at 2, 14, 21 and 60 days after birth, with evidence of cell death and changes in organelles consistent with degenerative processes. There was also a decrease in neurogenesis and changes in hippocampal volume in the anoxic animal compared to the control animal (Takada et al., 2015b). These results were obtained by different histological techniques (TUNEL, Fluorojade B), immunohistochemistry, transmission electron microscopy, stereology and magnetic resonance imaging. Also, cognitive deficits were found in the acquisition and performance of spatial and reference memory by Morris water maze. Takada et al., 2006), as well as an increase in anxiety in anoxic animals compared to controls, with high cross-mite larvae in P90 (Takada et al., 2015a).

Sex differences in the developing nervous system

The sexual dimorphism of the differences in neuronal organization existing between the brain of man and woman stem from several biological factors, which are subject to important hormonal regulation. Sex hormones influence the modeling of hemispheric differences to cognitive function (Witelson et al., 1976).

Differences related to brain injury, unilateral related to intelligence, presented ipsilateral neurological association in the injured male brain, whereas in the female brain the cognitive deficit is less asymmetrical (Inglis, 1981).

The sexual differentiation of the male nervous system depends on the determinant gene of the testes located on the Y chromosome (SRY gene), which is responsible for the development of the gonads and is regulated by the gonadal hormone. This hormone has regulatory effects on nerve tissue, depending on the stage of development (Andersson M et al., 1986). That Gene is expressed specifically in neurons expressing the enzyme tyrosine hydroxylase of the mesencephalic black substance. In an experimental study with male rats, suppression of the SRY gene results in motor deficit, although the number of neurons remains the same (Dewing P., 2006), which suggests the involvement of this gene with dopaminergic neurons of the male nigroestrial system . Female and male brain cells exhibit differences in the expression patterns of other genes that are specific to the developing brain, which determine specific functions and abilities for each genus (McCarthy, 2011).

Gender differences have been reported in locomotor activity (Bucci et al., 1995). Male rats perform better on tasks that require spatial abilities compared to females (Roof et al., 1993). However, interestingly, the male brain is more vulnerable to aggression than females in the critical period of development (Venderhus et al., 2010). Circulating testosterone in the newborn male, by not binding to alpha fetoprotein, can enter the nervous system through the blood-brain barrier and be converted into estrogen. The estrogenic organizing action occurs early, already between days 16 and 19 post-conception, immediately prior to the critical period of neural development, where it exerts irreversible effects and thus constitutes a substrate for gender variations. This data coupled with the high OBRb receptor expression in the thyroid of animals with restricted calorie and protein diet suggests inhibition of thyroid hormone release and a relation with altered somatic and developmental parameters (Valenzuela et al., 2014).

In the cellular genesis the gender differences appeared in the hippocampal volume and in the behavior as revealed by a study with neonatal hypoxia-ischemia model in rats. In this work, a significant increase in neurogenesis was demonstrated in females in relation to males (Waddell et al., 2015).

Hence our hypothesis is that rodent´s pups (30 hour of age), subjected to neonatal anoxia tend have white and gray matter injury in hippocampus and thining of corpus

callosum, ventroposteolateral thalamus nucleus, and substantia nigra compact dorsal altering motor and behavior along with nociceptive pathway of the pain.

II. JUSTIFICATION

Due to the clinical relevance of neonatal anoxia, the Neuroscience Laboratory adapted and developed the rodent anoxic animal model previously cited, validated by Takada et al., (2011). This model allowed to observe cytological alterations that indicated apoptosis, necrosis, autophagy and excitotoxicity in hippocampal cells later in adult rats, as well as memory deficits (Takada et al., 2015a). It also detected reduced hippocampal volume and decreased neurogenesis (Takada et al., 2015b). The early assessment of the severity of an acute brain injury, secondary to oxygen deprivation, provides an extremely useful basis for prevention and therapy in neonatology clinics (Naithani et al., 2010).

In agreement with the mentioned research, it has shown in humans that the ongoing changes in white matter brain, its matter microstructural changes, between 8 and 18 years of age, revealed by increased fractional anisotropy in the left frontal lobe, was positively correlated with the development of working memory capacity, while an increase in the left temporal lobe was associated with improvements in reading ability (Nagy et al., 2004). In addition, the different rates of myelination along the corpus callosum extent, highest during childhood (Keshavan et al., 2002), was also shown by fractional anisotropy (Lebel et al., 2012). These changes are speculated to relate to faster and more effective communication between brain regions, and reflect the increasing cognitive capacity seen during adolescence (Lenroot and Giedd, 2006) that might be disrupted by the neonatal anoxic insult with gender differences.

Therefore, aiming to explore the causes of the altered development observed in adolescent male and females, after neonatal anoxia (Kumar et al., 2017) in relation to the onset of ontogenetic reflexes and histological differences in the M1 and S1HL cortical layers, this study aims to explore how the neonatal anoxia affects sensory motor development in consideration to the related histological structure of substantia nigra compact dorsal, corpus callosum, as well as cognition in relation to the

hippocampal structure. To check impact on behavior and cognition we check different field of hippocampus and anoxia insult can influence the cell density in particular regions.Lastly we wanted to check impact on nociceptive pathway of pain and impact on ventro posterolateral thalamus nucleus.

III. OBJECTIVES

In order to contribute to the understanding of the sequelae of this injury and with the proposition of strategies and procedures to avoid or minimize its negative impacts, later in life, since it constitutes a worldwide clinical problem, the Neuroscience Lab team (ICB-USP), is making an effort in characterizing neonatal anoxia model, this study aims to explore its effects on the sensory motor development and behaviour in male and female Wistar rats.

1. Specific Objectives

1.1 To evaluate, the impact of neonatal anoxia on development of Sensory-motor abilities in male and female wistar rats along with the histological structure of Substantia Nigra Compact Dorsal (SNCD) and corpus callosum (cc).

1.2 To evaluate, the impact of neonatal anoxia on behavioral, cognitive and histological structure of hippocampus following neonatal anoxia in male and female wistar rats differences at adolescent age .

1.3 To evaluate, the impact of neonatal anoxia on mechanical pain histological structure of ventral posterolateral thalamus (VPL) nucleus.

Since the aim of the research is to approach both development and behaviour aspects of neonatal anoxia effects, this thesis is divided into three chapters to facilitate readers understanding and keep the focus as follows:

Chapter 1- Sex differences in neurological and motor development after neonatal anoxia in wistar rats.

Chapter 2- Sex difference in reference memory, anxiety and histological damage after neonatal anoxia in wistar rats.

Chapter 3-Sex differences in hypersensitivity to mechanical allodynia in wistar rats.

VII. General conclusion

Our findings demonstrate that for same degree of insult male rat deficits were different from female in somatic and motor development. Also, in reference memory and anxiety test anoxia has impaired the output and we see differences in male and female performances. In nociceptive perception of pain anoxia is hypersensitive and histologically male shows more damage in Ventroposterolateral nucleus. Histologically SNCD,cc, hippocampus,VPL was affected and male was vulnerable.

REFERENCES

Borlongan CV, Cahill DW, Sanberg PR. Locomotor and passive avoidance deficits following occlusion of the middle cerebral artery. Physiol Behav 1995;58:909–17.

Bucci Federica, Gemma Calamandrei, Aldina Venerosi, Igor Branchi, Flavia Chiarotti, Alessandra

Bustamante D, P. Morales, J.T. Pereyra, M. Goiny, M. Herrera-Marschitz Nicotinamide prevents the effect of perinatal asphyxia on dopamine release evaluated with in vivo microdialysis 3months after. birthExp. Brain Res., 177, pp.358–369,2007

Buwalda B, Nyakas C, Vosselman HJ, Luiten PG Effects of early postnatal anoxia on adult learningand emotion in rats. Behav Brain Res (1995) 67:85–90.

Buwalda B., Nyakas C., Vosselman H. J. And Luitmen P.G., Vasopressin prolongs behavioural and cardiac responses to mild stress in young but not in aged rats, Physiol. Behav., 1127-1131 (1992)

Cai, Z., Pang, Y., Xiao, F. & Rhodes, P.G. Chronic ischemia preferentially causes white matter injury in the neonatal rat brain. Brain (2001).Res. 898, 126–135.

Cannon M, Jones PB, Murray RM. Obstretic complications and schizophrenia: historical and metaanalytical review. Am J Psych 2002; 159:1080-92

Cannon TD, van Erp TG, Rosso IM, Huttunen M, Lonnqvist J, Pirkola T, Salonen O, Valanne L, Poutane VP, StandertskjoldNordenstam CG Fetal hypoxia and structural brain abnormalities in schizophreni patients, their siblings, and controls. Arch Gen Psychiatry(2002) 59:35–41.

Caputa M, Rogalska J, Wentowska K, Nowakowska A. Perinatal asphyxia, hyperthermia and hyperferremia as factors inducing behavioural disturbances in adulthood: a rat model. Behav Brain Res. 2005; 63 (2):24656.

Carthy LD, Margaret M. Steroids, sex and the cerebellar cortex: implications for human disease The Cerebellum– 38 47, 2008.

Casolini P, Zuena AR, Cinque C, Matteucci P, Alema GS, Adriani W. A subneurotoxic neonatal anoxia induces subtle behavioural changes and specific abnormalities in brain group-I metabtropic glutamate receptors in rat. J Neurochem 2005;95:137-45

Chavez-Valdez R, McGowan J, Cannon E, Lehmann CU Contribution of early glycemic status in the development of severe retinopathy of prematurity in a cohort of ELBW infants. J Perinatol (2011) 31:749-756.

Chen WF, Chang H, Wong CS, Huang LT, Yang CH. Impaired expression of postsynaptic density proteins in the hippocampal CA1 region of rats following perinatal hypoxia. Exp Neurol 2007;204:400-10

Cheng Y, Deshmukh M, D'Costa A, Demaro JA, Gidday JM, Shah A, Sun Y, Jacquin MF, Johnson Jr EM, Holtzman DM (1998) Caspase inhibitor affords neuroprotection with delayed administration in a rat model of neonatal hypoxic-ischemic brain injury. J Clin Invest 101:1992–1999.

Courville CB. Contributions to the study of cerebral anoxia. II. The mechanism and nature of consequentstructural alterations. Bull Los Angel Neuro Soc. 1950 Sep;15(3):129-54.

Cruz Ochoa NA, Ochoa-Amaya JE, V SL, Neonatal anoxia impairs long-term energy metabolism and somatic development of Wistar rats • InternationalJournal of Developmental Neuroscience 10.1016/ j.ijdevneu.2019.11.001

Daval JL, Vert P (2004) Apoptosis and neurogenesis after transient hypoxia in the developing rat brain.

Dell'Anna, E. Chen Y , Loidl F, Andersson K, Luthman J, Goiny M, Rawal R. E., CalzolarI, S., Molinari, M.; Luvone, L., & CalimicI, R. Delayed neuronal death following perinatal asphyxia in rat. Exp Brain Res 1997;115-15

Dell'Anna, M. E., CalzolarI, S., Molinari, M., Iuvone, L., & CalimicI, R.Development of monaamine system after neonatal anoxia in rats. Bains Res Bull 1993;32:159-70

Dell'Anna, M. E., CalzolarI, S., Molinari, M., Iuvone, L., & CalimicI, R. Neonatal anoxia induces transitory hyperactivity, permanent spatial memory deficits and CA1 cell density reduction in developing rats. Behavioural Brain Research, 45(2), 125-134. doi:10.1016/S0166-4328(05)800786, 1991.

Dewing P., Chiang CWK, Sinchak K, Sim H. Direct regulation of adult brain function by the malespecific factor SRY. Current Biology, 2006 .

Dobbing J, Smart JL. Vulnerability of developing brain and behaviour. Br Med Bull. 1974; 30(2):164-1971.

Fan L.W; PanY, Lin S, Tien L, T. Ma, P.G. Rhodes, Z. Cai Minocycline reduces rat J Neurosci lipopolysaccharide-induced neurological dysfunction and brain injury in the neonatal Res, 82 , pp. 71–82, 2005.

Fan LW, Lin S, Pang Y, Lei M, Zhang F, Rhodes PG, Cai Z (2005a) Hypoxia-ischemia induced neurological dysfunction and brain injury in the neonatal rat. Behav Brain Res 165:80-90.

Fan LW, Lin S, Pang Y, Lei M, Zhang F, Rhodes PG, Cai Z (2005a) Hypoxia-ischemia induced neurological dysfunction and brain injury in the neonatal rat. Behav Brain Res 165:80-90.

Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 1998; 44:951-8

Felix-Ortiz, A.C., Beyeler, A., Seo, C., Leppla, C.A., Wildes, C.P., and Tye, K.M. (2013). BLA to vHPC inputs modulate anxiety-related behaviors. Neuron 79, 658-664.

Felt BT, Schallert T, Shao J, Liu Y, Li X, Barks JD. Early appearance of functional deficits after neonatal excitotoxic and hypoxic–ischemic injury: fragile recovery after development and role of the NMDA receptor. Dev Neurosci 2002;24:418–25.

Flandreu El Kerry J. Ressler, , Michael J. Owensd, , Charles B.Nemeroffe). Chronic overexpression of corticotropin-releasing factor from the central amygdala produces HPA axis hyperactivity and behavioral anxiety associated with gene-expression changes in the hippocampus and paraventricular nucleus of the hypothalamus psychoendocrinology 37,27-30,2012.

Flandreu Nyakas, C., Buwalda, B. Markel, E., Korte, S.M., & Luiten, P.G. Life-spanning behavioural and adrenal dysfunction Effect of prenatal hypoxia on brain development induced by prenatal hypoxia in the rat is prevented by the calcium antagonist .European Journal of Neuroscience, 6, 746–753, 1994

Forger NG, Rosen GJ, Waters EM, Jacob D, Simerly RB, de Vries GJ. Deletion of Bax eliminates sex differences in the mouse forebrain. Proc Natl Acad Sci U S A 101:13666–13671, 2004.

Frye CA; Walf AA A Review and Update of Mechanisms of Estrogen in the Hippocampus and Amygdala for Anxiety and Depression Behavior Neuropsychopharmacology volume31, pages1097–1111 (2006)

Funayama CAR. Anóxia neonatal e seqüelas neurológicas. Campinas, SP: Ed Átomo, 2005.

Galeano P, Blanco E, Logica Tornatore TM, Romero JI, Holubiec MI, Rodriguez de Fonseca F, Capani F (2014) Life-long environmental enrichment counteracts spatial learning, reference and working memory deficits in middle-aged rats subjected to perinatal asphyxia. Front Behav Neurosci 8:406.

Grafe MR. Developmental changes in the sensitivity of the neonatal rat brain to hypoxic/ischemic injury. Brain Res 1994;653:161–6.

Hagan P, Barks JD, Yabut M, Davidson BL, Roessler B, Silverstein FS (1996) Adenovirus-mediated over-expression of interleukin-1 receptor antagonist reduces susceptibility to excitotoxic brain injury in perinatal rats. Neuroscience 75:1033–1045.

Hedner T, Lundborg P. Serotonin metabolism in neonatal rat brain during asphyxia and recovery. Acta Pysiol Scand 1980:109:163-8.

Hermans RH, Hunter DE, McGivern RF, Cain CD, Longo LD. Behavioural sequelae in young rats of acute intermittent antenatal hypoxia, Neurotoxical Teratol 1992; 14: 119-29

Herrera Marschitz M. Perinatal asphyxia: CNS development and deficits with delayed onset. Front Neurosci 8:47, 2014.

Hill CA, S.W.Threlkeld and R.H.Fitch. “Early testosterone modulated sex differences in behavioral outcome following neonatal hypoxia ischemia in rats,” International Journal of Developmental Neuroscience, vol. 29, no. 4, pp. 381–388, 2011.

Huang HZ, Wen XH, Liu H (2016) Sex differences in brain MRI abnormalities and neurodevelopmental outcomes in a rat model of neonatal hypoxia-ischemia. Int J Neurosci 126:647-657.

Hurn PD, Vannucci SJ, Hagberg H. Adult or perinatal brain injury: does sex matter? Stroke 2005;36(2):193–5. doi: 10.1161/01.STR.0000153064.41332.f6.

Huttenlocher PR, Raichelson RM. Effects of neonatal hemispherectomy on location and number of corticospinal neurons in the rat. Dev Brain Res 1989;47:59–69.hypothermia after neonatal hypoxiaischemia: short- and long-term outcome. Pediatr Res 43:738-745.

Ikeda T1, Mishima K, Yoshikawa T, Iwasaki K, Fujiwara M, Xia YX, Ikenoue T. Selective and long-term learning impairment following neonatal hypoxic-ischemic brain insult in rats.Behav Brain Res. 2001 Jan 8;118(1):17-25.

Inglis W. Sex differences in the effects of unilateral brain damage on intelligence. Science 212:693-695,1981.

IshikawaM., Takayuki Ohira, Jun Namiki,, Masato Kobayashi, Electrophysiological investigation ofhemifacial spasm after microvascular decompression: F waves of the facial muscles, blink reflexes, and abnormal muscle responses. Journal of Neurosurgery 1/ Vol. 86 / No. 4 / Pages 654661, 1997.

Luvone L, Geloso MC, Dell‘Anna E. Changes in open field behavior, spatial memory, and hippocampal parvalbumin immunoreactivity following enrichment in rats exposed to neonatal anoxia. Exp Neurol 1996;139:25–33.

Jansen EM, Low WC. Long-term effects of neonatal ischemichypoxic brain injury on sensorimotor and locomotor tasks in rats. Behav Brain Res 1996;78:189–94.

Jansen EM, Low WC. Long-term effects of neonatal ischemichypoxic brain injury on sensorimotor and Jansen EM, Low WC. Quantitative analysis of contralateral hemisphere hypertrophy and sensorimotor performance in adult rats following unilateral neonatal ischemic-hypoxic brain injury. Brain Res 1996;708:93–9.

Jansen EM, Solberg L, Underhill S, Wilson S, Cozzari C, Hartman BK, Faris PL, Low WC. Transplantation of fetal neocortex ameliorates sensorimotor and locomotor deficits following neonatal ischemic-hypoxic brain injury in rats. Exp Neurol 1997;147:487–97.

Johnston MV (2001) Excitotoxicity in neonatal hypoxia. Ment Retard Dev Disabil Res Rev 7:229–234.

Kartje-Tillotson G, Neafsey EJ, Castro AJ. Electrophysiological analysis of motor cortical plasticity after cortical lesions in newborn rats. Brain Res 1985;332:103–11.

Kheirbek, M.A., Klemenhagen, K.C., Sahay, A., and Hen, R. (2012). Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. Nat Neurosci 15, 16131620.

Khong PL, Lam BC, Tung HK, Wong V, Chan FL, Ooi GC. MRI of neonatal encephalopathy. Clin Radiol. 2003 Nov;58(11):833-44.

Kjaerby, C., Athilingam, J., Robinson, S.E., Iafrati, J., and Sohal, V.S. (2016). Serotonin 1B Receptors Regulate Prefrontal Function by Gating Callosal and Hippocampal Inputs. Cell Rep 17, 28822890.

Kjelstrup, K.G., Tuvnes, F.A., Steffenach, H.A., Murison, R., Moser, E.I., and Moser, M.B.Krishnan .V, M.H. Han, M. Mazei-Robison, S.D. Iniguez, J.L. Ables, V. Vialou, O. Berton, S. Ghose, H.E. Covington III, M.D. Wiley, R.P. Henderson, R.L. Neve, A.J. Eisch, C.A. Tamminga, S.J. Russo, C.A. Bolanos, E.J. NestlerAKT signaling within the ventral tegmental area regulates cellular and behavioral responses to stressful stimuli. Biol. Psychiatry, 64 (8) pp. 691–700, 2008.

Krishnan .V, M.H. Han, M. Mazei-Robison, S.D. Iniguez, J.L. Ables, V. Vialou, O. Berton, S. Ghose,

H.E. Covington III, M.D. Wiley, R.P. Henderson, R.L. Neve, A.J. Eisch, C.A. Tamminga, S.J. Russo, C.A. Bolanos, E.J. NestlerAKT signaling within the ventral tegmental area regulates cellular and behavioral responses to stressful stimuli. Biol. Psychiatry, 64 (8) pp. 691–700, 20

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Kurinczuk,JJ.,White KM, Badawin N. Epidemiology of neonatal encephalopathy. Early human development. 86; 329-338, 2010.

Larroche JC. Massive cerebral necrosis in newborn infants. Its relation to maturation, its clinical and bioelectric symptoms. Biol Neonat 1968; 13: 340–6

Laviola G, Adriani W, Rea M, Aloe L, Alleva E. Social withdrawl, neophobia, and stereotyped behavior in developing rat exposed to neonatal asphyxia. Psychopharmacology 2004; 175:196-205

Lawn JE, Cousens S, Zupan J, Team LNSS. 4 million neonatal deaths: When? Where? Why? Lancet. 365:891–900, 2005.

Lengvari, D. Reglodi.Changes in open-field activity and novelty-seeking behavior in periadolescent lesions. Nature. 297(5868):681-33,1982.

Liam J. Drew SF, Rene S. Adult neurogenesis in the mammalian hippocampus: Why the dentate gyrus? Hen1,2,3,6 1Division of Integrative Neuroscience, Research Foundation for Mental Hygiene, New York State Psychiatric Institute, New York 10032, USA; 2Department of Psychiatry, Columbia University,New York 10032, USA; 3Department of Neuroscience, Columbia University, New York 10032, USA; 4Center for Theoretical Neuroscience, Columbia University, New York 10032, USA.

Limperopoulos C, Benson CB, Bassan H, Disalvo DN, Kinnamon DD, Moore M, Ringer SA, Volpe JJ, du Plessis AJ 2005 Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. Pediatrics 116:717–724

Limperopoulos C, Soul JS, Haidar H, Huppi PS, Bassan H, Warfield SK, Robertson RL, Moore M, Akins P, Volpe JJ, du Plessis AJ 2005 Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics 116:844–850

Liu JP, Chang LR, Gao XL, Wu Y (2008) Different expression of caspase-3 in rat hippocampal subregions during postnatal development. Microsc Res Tech 71:633–638.

Liu XH,EunBL,SilversteinFS,BarksJD (1996) Theplatelet-activating factor antagonist BN 52021 attenuates hypoxic-ischemic brain injury in the immature rat. Pediatr Res 40:797–803. Liu XH,

Kwon D, Schielke GP, Yang GY, Silverstein FS, Barks JD (1999) Mice deficient in interleukin-1 converting enzyme are resistant tone on at a lhypoxic-ischemic brain damage.J Cereb Blood Flow Metab 19:1099–1108.

Lubics A, Dora R. Neurological Reflexes and early motor. Perinatal brain damage behaviour in rats subjected to neonatal hypoxic Ischaemia. Behavior Brain Research 157157-165, 2005.

Lynch JK, Epidemiology and classification of perinatal stroke. Seminars in Fetal & Neonatal Medicine.; 14:245–249, 2009.

Dell'Anna ME, Neonatal anoxia induces transitory hyperactivity, permanent spatial memory deficits and CA1 cell density reduction in developing rats, Behav. Brain Res. 45 (2) (1991) 125–134.

Majeed R, Memon Y, Majeed F, Shaikh NP, Rajar UD. Risk factor of birth asphyxia. J Ayub Med coll Addottabad 2997; 19:67-71

Markgraf CG, Green EJ, Hurwitz BE, Morikawa E, Dietrich WD, McCabe PM, Ginsberg MD, Schneiderman N. Sensorimotor and cognitive consequences of middle cerebral artery occlusion in rats. Brain Res 1992;575:238–46.

Marlow N, Rose AS, Rands CE, et al. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed 2005;90(5):F380–7. doi: 10.1136/adc.2004.067520.

Marschitz H; Tanya N, Edgardo R M, Pablo E M, Daniela E, Ronald P, Valentina M, Manuel. G-H, Benjamin R, Nicola S, Diego B, Paola M and Peter J. Gebicke-Perinatal asphyxia: CNS development and deficits with delayed onset. Fronteirs in Neuroscience, 2014.

Martin LJ (1999) Neuronal death in amyotrophic lateral sclerosis is apoptosis: possible contribution of a programmed cell death mechanism. J Neuropathol Exp Neurol 58:459–471.

Martin,LJ. BrambrinkAM, KoehlerRC, TraystmanRJ (1997a) Primary sensory and forebrain motor systems in the newborn brain are preferentially damaged by hypoxia-ischemia. J Comp Neurol 377:262–285.

MartinLJ,BrambrinkAM,LehmannC,Portera-CailliauC,KoehlerRC, Rothstein J, Traystman RJ (1997b) Hypoxia-ischemia causes abnormalities in glutamate transporte rs and death of astroglia and neurons in newborn striatum. Ann Neurol 42:335–348.

Mason CA, Gregory E.J Maturation and synaptogenesis Neurosci. Jul;4(7):1715-35, 1984.

McDonald W, M.V. Johnston Physiological and pathophysiological roles of excitatory amino acids during central nervous system development Brain Research Review, 15 pp. 41–70, 1980.

Messerschmidt A, Fuiko R, Prayer D, Brugger PC, Boltshauser E, Zoder G, Sterniste W, Weber M, Birnbacher R 2008 Disrupted cerebellar development in preterm infants is associated with impaired neurodevelopmental outcome. Eur J Pediatr 167:1141–1147

Mikati MA, Zeinieh MP, Kurdi RM, Harb SA. Long term effects of acute and chronic hypoxian on behaviour and on hippocampal histology in the developing brain. Develop Brain Res 2005;157:98-102

Ming-Yan H, Luo YL, Zhang XC, Liu H, Gao R, Wu JJ.Hypoxic-ischemic injury decreases anxiety-like behavior in rats when associated with loss of tyrosine-hydroxylase immunoreactive neurons of the substantia nigra.Braz J Med Biol Res. 2012 Jan;45(1):13-9. Epub 2011 Dec 9.PMID:22147192.

Moore- Bradley V.S. Ten, M., J.A. Gingrich, R.I. Stark, D.J. Pinsky .Brain injury and neurofunctional deficit in neonatal mice with hypoxic–ischemic encephalopathy .Behav Brain Res, 145 pp. 209–219, 2003.

Morozova EA, Belousova MB. Attention deficit hyperactivity syndrome: evolution, clinical presentations, treatment. Zh Nevrol Psikhiatr Im S S Korsakova. 2009;109(2):31-4.

Morris RG, Garrud P, Rawlins JN, Keefe,O. Place navigation impaired in rats with hippocampal

Mosgoeller,Gert Lubec), Long term neurological and behavioral effects of graded perinatal asphyxia in the rat .Long term neurological and behavioural effects of graded perinatal asphyxia in rats. Life sciences vol 66,Issue 10, pg 947-962,2000

Nakamura Y, Nakashima T, Fukuda S, Nakashima H, Hashimoto T. Hypoxic-ischemic brain lesions found in asphyxiating neonates. Acta Pathol Jpn. 1986 Apr;36(4):551-63.

Northington FJ, Ferriero DM, Graham EM, Traystman RJ, Martin LJ (2001) Early Neurodegeneration after Hypoxia-Ischemia in Neonatal Rat Is Necrosis while Delayed Neuronal Death Is Apoptosis. Neurobiol Dis 8:207-219.

Nyakas C., Buwalda, B., & Luiten, P.G. Hypoxia and brain development.. Progress in Neurobiology, 49, 1–51, 1996.

Nyakas, C., Buwalda, B. Markel, E., Korte, S.M., & Luiten, P.G. Life-spanning behavioural and adrenal dysfunction Effect of prenatal hypoxia on brain development induced by prenatal hypoxia in the rat is prevented by the calcium antagonist .European Journal of Neuroscience, 6, 746–753, 1994.

Okoshi, Y., Itoh, M., Takashima, S.,. Characteristic neuropathology and plasticity in periventricular leukomalacia. Pediatr. Neurol. (2001) 25, 221–226.

Padilla-Coreano, N., Bolkan, S.S., Pierce, G.M., Blackman, D.R., Hardin, W.D., Garcia-Garcia, A.L., Spellman, T.J., and Gordon, J.A. (2016). Direct Ventral Hippocampal-Prefrontal Input Is Required for Anxiety-Related Neural Activity and Behavior. Neuron 89, 857-866.

Parfitt, G.M., Nguyen, R., Bang, J.Y., Aqrabawi, A., Tran, M.M., Seo, D.K., Richards, B.A., and Kim, J.C. (2017). Bidirectional Control of Anxiety-Related Behaviours in Mice: Role of Inputs Arising from the Ventral Hippocampus to the Lateral Septum and Medial Prefrontal Cortex. Neuropsychopharmacology.

Paxinos G. The Rat Nervous System. 3. Ed. London: Elsevier Academic Press,. 2004; 1280.

Perrin D, Mamet J, Scan H, Roux JC, Berod A,Dalmaz Y.Long term prenatal hypoxia alters maturation of brain catecholaminergic system and motor behaviors in rats synapses 54:92-101, 2004.

Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long term cognitive outcome in preterm infants. JAMA. 2000;284(15):1939-1947.

Polley DB, Kvasnák E, Frostig Naturalistic experience transforms sensory maps in the adult cortex of caged animals. Nature.;429 (6987):67-71, 2004.

Puyal J, Ginet V, Clarke PG (2013) Multiple interacting cell death mechanisms in the mediation of excitotoxicity and ischemic brain damage: a challenge for neuroprotection. Prog Neurobiol 105:24–48.

Rakic P, Sidman RL. Histogenesis of cortical layers in human cerebellum, particularly the lamina dissecans. J Comp Neurol 1970; 139: 473–500

Reglodi D, Kiss P, Tamas A, Lengvari I. The effects of PACAP and PACAP antagonist on the neurobehavioral development of newborn rats. Behav Brain Res 2003;140:131–9.

Reglodi D, Tamas A, Somogyvari-Vigh A, Szanto Z, Kertes E, Lenard L, Arimura A, Lengvari I. Effects of pretreatment with PACAP on the infarct size and functional outcome in rat permanent focal cerebral ischemia. Peptides 2002;23:2227–34.

Reinoso BS, Castro AJ. A study of corticospinal remodelling using retrograde fluorescent tracers in rats. Exp Brain Res 1989;74:387–94.

Renolleau S, S. Fau, C. Goyenvalle ."Specific caspase inhibitor Rice D., Barone S Jr, Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environment Health Perspective; 108:511–533, 2000.

Rogalska J, Caputa M, Wentowska K, Nowakowska A. Stress induced behavior in adult and old rats: effect of neonatal asphyxia, body temperature, and chelatonin of iron. J Physiology Pharmacology 2006; 57:17-34

Rogalska J, Danielisova V, Caputa M (2006) Effect of neonatal body temperature on postanoxic, potentially neurotoxic iron accumulation in the rat brain. Neurosci Lett 393:249–254.

Rogers DC, Campbell CA, Stretton JL, Mackay KB. Correlation between motor impairment and infarct volume after permanent and transient middle cerebral artery occlusion in the rat. Stroke 1997;28:2060–6.

Roland EH, Poskitt K, Rodriguez E, Lupton BA, Hill A (1998) Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging [see comments]. Ann Neurol 44:161–166.

Roof L.R, The dentate gyrus is sexually dimorphic in prepubescent rats: testosterone plays a significant role. Brain Res. 610, 148–151, 1993.

Rosenberg PA, Aizenman E. Hundred-fold increase in neuronal vulnerability to glutamate

Roy V, Chapillon P. Further evidences that risk assessment and object exploration behaviours are useful to evaluate emotional reactivity in rodents. Behav Brain Res. 154:439-448,2004.

Sanches EF1, Arteni NS, Nicola F, Boisserand L, Willborn S, Netto CA. Early hypoxia-ischemia causes hemisphere and sex-dependent cognitive impairment and histological damage. Neuroscience. 2013 May 1;237:208-15. doi: 10.1016/j.neuroscience.2013.01.066.

Schumacher A, Vlassov E, Ito R.The ventral hippocampus, but not the dorsal hippocampus is critical for learned approach-avoidance decision making.Hippocampus. 2016 Semin Perinatol 28:257–263.

Schwaller F,Fitzgerald M. The consequences of pain in early life: injury-induced plasticity in developing pain pathways. European Journal of Neuroscience, Vol. 39, pp. 344–352, 2014

Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ (2013) Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol 106–107:1–16.

Shahrokhi N, Khaksari M, Soltani Z, Mahmoodi M, Nakhaee N. Effect of sex steroid hormones on brain edema, intracranial pressure, and neurologic outcomes after traumatic brain injury. Can J Physiol Pharmacol. 2010; 88:414–21.

Shors TJ, Seib TB, Levine S, Thompson RF (1989) Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. Science 244:224–226.

Shuey, D.L.; Sadler, T.W.; Tamir, H.; Lauder, J.M. Serotonin as a regulator of morphogenesis: site specific malformations following exposure to serotonin uptake inhibitors. Teratology, v. 46, p. 367–378, 1992.

Simola, N., Bustamente, D., Pinna, A., Pontis., Morales, P., Morelli, M., Herrera- Marschitz, M.,. Acute perinatal asphyxia impairs non spatial memory and alters motor cordination in adult male rats. Exp. Brain Res 185, 595-601 (2008).

Sivakumar, V., Lu, J., Ling, E.A., Kaur, C.,. Vascular endothelial growth factor andnitric oxide production in response to hypoxia in the choroid plexus in neonatal brain. Brain Pathol. 18, 71–85 (2008).

Souza A, Dussan-Sarria JA, Medeiros LF, Souza AC, Oliveira C, Scarabelot VL, Adachi LN, Winkelmann-Duarte EC, Philippi-Martins BB, Netto CA, Caumo W[2], Torres IL. Neonatal hypoxic-ischemic encephalopathy reduces c-Fos activation in the rat hippocampus: evidence of a long-lasting effect. Int J Dev Neurosci. 2014 Nov;38:213-22. doi: 10.1016/j.ijdevneu.2014.09.003.

Stewart AL, Rifkin L, Amess PN, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet. 1999;353:1653-1657.

Takada SH, dos Santos Haemmerle CA, Motta-Teixeira LC, Machado-Nils AV, Lee VY, Takase LF, Cruz-Rizzolo RJ, Kihara AH, Xavier GF, Watanabe IS, Nogueira MI (2015) Neonatal anoxia in rats: hippocampal cellular and subcellular changes related to cell death and spatial memory. Neuroscience 284:247-259.

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 (2016) Impact of neonatal anoxia on adult rat hippocampal volume, neurogenesis and behavior. Behav Brain Res 296:331-338.

Takada SH, Sampaio CA, Allemandi W, Ito PH, Takase LF, Nogueira MI (2011) A modified rat model of neonatal anoxia: Development and evaluation by pulseoximetry, arterial gasometry and Fos immunoreactivity. J Neurosci Methods 198:62-69.

Ten, M Moore- Bradley V.S., J.A. Gingrich, R.I. Stark, D.J. Pinsky .Brain injury an neurofunctional deficit in neonatal mice with hypoxic–ischemicencephalopathy Behav Brain Res, 145 pp. 209–219, 2003 10825-10830.

Tien LT, Park Y, Fan LW, Ma T, Loh HH, Ho IK. Increased dopamine D2 receptor binding and enhanced apomorphine-induced locomotor activity in mu-opiod receptor knock out mice. Brain Res Bull 2003;61:109-15

Tomimatsu T, Fukuda H, Endoh M, Mu J, Watanabe N, Kohzuki M, Fujii E, Kanzaki T, Oshima K, Doi K, Kubo T, Murata Y. Effects of neonatal hypoxia- ischemic brain injury on skilled motor tasks and brainstem function in adult rats. Brain Res 2002;926:108–17.

Tuor UI, Chumas PD, Del Bigio MR. Prevention of hypoxic– ischemic damage with dexamethasone is dependent on age and not influenced by fasting. Exp Neurol 1995;132:116–22.

Van de Berg, W,D., Blockland, A., Cuello, A.C., Schimtz, C., Vreuls W. Perinatal asphyxia results in changes in GABAergic and locomotor system (2003). Neuroscience 117, 83-96

Van der Staay FJ, Augstein KH, Horvath E. Sensorimotor impairments in Wistar Kyoto rats with cerebral infarction, induced by unilateral occlusion of the middle cerebral artery: recovery of function. Brain Res 1996;715:180–8.

Vannucci RC. Hypoxic-ischemic encephalopathy. Am J Perinatol. 2000;17(3):113-20.

Vannucci RC., Experimental models of perinatal hypoxic-ischemic brain damage, APMIS, 40: 8995,1999.

Vasconcelos, R., 2013. Effect of the influence of neonatal anoxia on maternal behavior and somatic and sensorimotor development of Wistar rats. University of Sao Paulo.

Venderhus, Markestad, A Martin, L Johnson, P Coker-Bolt A Case Exploration of Early Motor Delays in an Extremely Premature InfantJournal of Pediatrics, 159(1): 79–85. 2010.

Venerosi A., Cutuli D., Chiarotti F., Calamandrei G. C-section birth per se or followed by acute global asphyxia altered emotional behaviour in neonate and adult rat. Behavioural Brain Research 168 (1), 56-63, ISSN 0166-4328, 2006.

Verdina, And Enrico Alleva. Effects of Prenatal AZT on Mouse Neurobehavioral Development and Passive Avoidance Learning. Neurotoxicology and Teratology, Vol. 21, No. 1, pp. 29–40 (1995).

Verma P, Hellemans KG, Choi FY, Yu W, Weinberg J.Circadian phase and sex effects on depressive/anxiety-like behaviors and HPA axis responses to acute stress.Physiol Behav. 2010 Mar 3;99(3):276-85. doi: 10.1016/j.physbeh.2009.11.002. Epub 2009 Nov 27.PMID:19932127.

Vexler ZS Van Velthoven CT, Sheldon RA, Kavelaars A, Derugin N. Molecular and biochemical mechanism of Post anoxic Brain Injury ; 44(5):1426-32. 2013.

Volpe JJ (1995) Neurology of the newborn, pp 314–369. Philadelphia: Saunders.

Volpe JJ. Brain injury in the premature infant: overview of clinical aspects, neuropathology, and pathogenesis. Semin Pediatr Neurol. 5(3):135-51, 1998.

Volpe JJ. Perinatal hypoxic-ischemic brain damage. J NeuroSci Res 2001. W.B. Saunders, pp 217–396.

Volpe JJ., Cerebral white matter injury of the premature infant-mor common than you think.Pediatrics.; 112:176–180, 2003.

VolpeJJ Pasternak JF ,Parasagittal cerebral injury in neonatal hypoxic-ischemic encephalopathy: clinical and neuroradiologic features. *Pediatric Research* volume11, page 566 (1977)

Waddell J, Hanscom M, Shalon Edwards N, McKenna MC, McCarthy MM (2016) Sex differences in cell genesis, hippocampal volume and behavioral outcomes in a rat model of neonatal HI. Exp Neurol 275 Pt 2:285-295.

Waddell J., Marie Hanscom, Sex differences in cell genesis, hippocampal volume and behavioural outcomes in a rat model of neonatal HI. Experimental Neurology 275, 2016.

Wagner BP, Nedelcu J, Martin E. Delayed postischemic hypothermia improves long-term behavioural outcome after cerebral hypoxia–ischemia in neonatal rats. Pediatr Res 2002;51:354– 60.

Wagner F ;Evelin L; Schaeffer ; Franziska ; Angelika Schmitt ; Gattaz ; Oliver Gruber ;Thomas Schneider-Axmann ; Peter Falkai ; Andrea SchmittIncreased cell proliferation in the rat anterior cingulate cortex following neonatal hypoxia: relevance to schizophrenia J Neural Transm 120:187– 195, 2013.

Wainwright MS, Craft JM, Griffin ST, Marks A. Increased susceptibility of s100B transgenic mice to perinatal hypoxia-ischaemia. Ann Neurol 2004;56:61-7

Walker, S.M. (2013) Long-term effects of early pain and injury: animal models. In McGrath, P.J., Walker, S.M., Stevens, B.J. & Zempsky, W.T. (Eds), Oxford Textbook of Paediatric Pain. OUP, Oxford, pp. 20–29.

Wasterlain CG, Hattori H, Yang C et al. Selective vulnerability of neuronal subpopulations during ontogeny reflects discrete molecular events associated with normal brain development. In: Neonatal Seizures, Eds CG Wasterlain, P Vert. New York: Raven Press, 1990: 69–81

Winocur G, Wojtowicz JM, Sekeres M, Snyder JS, Wang S (2006) Inhibition of neurogenesis interferes with hippocampusdependent memory function. Hippocampus 16:296–304.

Winter, B., Juckel, G., Voktorov, I., Katchanov, J., Gietz, A. & Sohr, R. (2005) Anxious and hyperactive phenotype following brief ischemic episodes in mice. Biol. Psychiatry., 57, 1166–1175.

Witelson DF.,Sex and the single hemisphere: Specialization of the right hemisphere for spatial processing.Science, 1976 .

Wu, M.V., and Hen, R. (2014). Functional dissociation of adult-born neurons along the dorsoventral axis of the dentate gyrus. Hippocampus 24, 751-761.

Xavier GF., Francisco J.B, Oliveira F, Andre´MG. Dentate Gyrus-Selective Colchicine Lesion and Disruption of Performance in Spatial Tasks: Difficulties in ‘‘Place Strategy’’ Because of a Lack of Flexibility in the Use of Environmental Cues? HIPPOCAMPUS 9:668–681,1999.

Y. Sanghee,Ryan, R. Irene, M.Amelia J Eisch.Re-evaluating the link between neuropsychiatric disorders and dysregulated adult neurogenesis.*Nature Medicine* volume22, (2016) pages1239–1247 2014

Yang S. H., E. Perez, J. Cutright .Testosterone increases neurotoxicity of glutamate in vitro and ischemia-reperfusion injury in an animal model," Journal of Applied Physiology,vol. 92, no. 1, pp. 195–201, 2002.

Yang T, Zhuang L, Terrando N, Wu X, Jonhson MR, Maze M, Ma D (2011) A clinically relevant model of perinatal global ischemic brain damage in rats. Brain Res 1383:317–323.

Zhang Z,W, (2006) Postnatal development of the mammalian neocortex: Role of activity revisited.Canadian Journal of Neurological Science, 33), pp. 158–169.

Zhu C, Wang X, Xu F, Bahr BA, Shibata M, Uchiyama Y, Hagberg H, Blomgren K (2005) The influence of age on apoptotic and other mechanisms of cell death after cerebral hypoxia-ischemia. Cell Death Differ 12:162-176.