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Effects of Pre- and Neonatal Undernutrition on Long-Term Hearing Cognition of the Rat

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Abstract

Experimental evidence in the rat suggests that perinatal undernutrition, associated with sensory and hormonal deficiencies, interferes with brain network integrative actions. We review peripheral and central morpho-functional alterations related to early food restriction along with the auditory relays, and their connections with the limbic system, which are essential for motivation-emotional arousal. The findings indicated that different morpho-functional alterations in the auditory system permanently affect the brainstem, the reticular thalamic nucleus, and the prefrontal and auditory cortices. Moreover, data showed the noxious role of early food restriction and the external ear occlusion on the distal portions of dendritic arbor measurements, in the cochlea, nucleus ambiguous and motor cortical pyramids. These anatomical alterations also correlated with deficiencies in the dynamic motor and auditory cognitive brain plasticity. Food restriction-related deficiencies in the motor-emotional-behavioral arousal systems may be useful to understand long-term cognitive disorders in humans.

Keywords

Perinatal Undernutrition, Auditory Cognition, Mother-Litter Bonds, Rats

1. Introduction

The auditory system and its function in the rat develop late during the gestational period, achieving maturity until postnatal day (PD) sixteen. The auditory system plays a critical role in the early orientation of head and body movements to novel stimuli, not within the field of view. Additionally, it is essential for mother-litter bonds, social communication and in humans for music perception, mood, and other affective states [1] [2]. This system is organized in a complex neuronal network that starts with the outer cochlear receptors, which are connected to a chain of brainstem structures, which ascend neural coded signals to the thalamus and auditory cortex. As in other sensory systems, the neocortex is an organ for the higher integration of afferent signals, underlying motor activities, autonomic responses, and complex cognitive abilities, because of the activation of ancient limbic territories that we share with other species to generate affective states [3] [4]. Because the auditory system is influenced by multiple factors including other sensorial inputs, perinatal food supply, environmental sound processing, and morphogenetic hormones among others, the facts and new concepts need to be revisited, particularly around perinatally disturbances with long-lasting effects on brain capabilities. Researching the disruption of these complex interactions during critical stages of life is relevant to analyze the long-term consequences on normal and pathological cognitive responses in animals or humans [5] [6] [7] [8] [9]. Moreover, the study of auditory cognition early in life is fundamental to understand how music can influence a person's mood and emotional expressions and induce pleasure or calm to relieve psychological stress.

Prenatal impairment indexes have shown that, in altricial species, perinatal food restriction severely affects birth weight, body size, milk consumption and newborn suckling activity. Moreover, complex environmental deficiencies during the neonatal period, adolescence, and young adulthood have correlated with environmental factors that alter neuronal networks underlying cognitive responses [5] [10] [11]. These epigenetic factors, including early food restriction, disrupt the axonal conduction of electrical activity discharges at different brain levels by decreasing neurogenesis, dendritic density, spines, and synaptic contacts of brain structures, resulting in abnormal transmission of sensory ascending signals from subcortical-cortical and cortical descending brain stem performance [12]-[17]. Brain damage early in life, associated with neonatal undernutrition, increases secondary hypothyroidism and the morpho-functional severity of these influences correlate with different long-term activities. These dual concurrent interactions have resulted in neuronal atrophy, delayed migration, differentiation, connectivity, poor myelination and disrupted adult cognitive performance [18]-[24]. Additionally, early undernutrition disrupts the hypothalamic-pituitary-adrenal axis by affecting the feedback mechanisms, since fetal programming interferes with both short- and long-term adaptive responses to stress [25] [26] [27] [28] [29]. The aim of this review was to examine the association between perinatal undernutrition and long-term auditory cognition in rats.

2. Early Morpho-functional Brain Alterations

Underfed peripheral sensory deficiencies

Direct physical exploration and electrophysiological analysis of rodents indicated that sensory systems normally emerge following a sequential order, starting with the sensorimotor channel, followed by the olfactory, gustatory, auditory, and visual channels, affected by perinatal undernutrition [13] [26] [30] [31] [32]. In the rat, ear-opening normally begins on PD 11 and reaches maturity until PD 13, with the development of head orientation in response to auditory stimulation [33]. By contrast, early underfed rats present delayed ear-opening, which initiates on PD 12 and matures until PD 15 [34].

The delayed physical maturation of the external auditory canal also depends on the action of reduced thyroid hormone levels, whose actions are more active by early nutritional deficiencies because their synergistic morphogenetic role in the peripheral and central auditory structures of the brain [18] [35] [36]. However, little is known about the mechanisms underlying the effects of these synergic epigenetic factors on cognitive functions at later ages along the auditory neuronal sensory relays. In the rat brain, the critical period of thyroid hormone secretion initiates around gestational day 18 (GD 18) and continuous until PDs 21 - 25 [37]. Before the GD 18 the fetus depends on the maternal thyroid secretion for brain development, and most morphogenetic disorders associated with perinatal undernutrition and early hypothyroidism are seen in structures that mature after birth [37] [38].

Experimental studies on the administration of propylthiouracil (PTU) in pregnant dams showed morpho-functional damage in the progenies' organ of Corti, including inner column growth and tectorial membrane distortions that affect the delicate contacts with external hair cells to fire electrical impulses [39] [40]. Furthermore, these cochlear alterations are associated with delayed auditory righting reflex and startle responses, and open-field exploratory deficits [41]. Moreover, rats were given PTU in drinking water at different concentrations from gestation day 18, until PD 21. Results showed serum thyroxine reductions at 5 and 25 ppm PTU in the PDs 1, 7, 14 and 21 groups. T3 hormone was also reduced for all ages ≥ 7 at 25 ppm with rats also presenting delayed eye-opening, body weight, and preweaning motor activity, and postweaning hyperactivity. Reflex audiometry indicated threshold auditory deficits in adult rats receiving 5 and 25 ppm of PTU. These consistent results showed the high thyroid vulnerability and elevated auditory and motor responses to mild hypothyroidism [42]. In summary the interaction between the early hypothyroidism and mild or severe perinatal undernutrition, results relevant because frequently is place obliquely for instance in the newborn body measurements and ultrasound deficiencies during the assessment of maternal behavior [24].

In summary, although cochlear damages associated to early undernutrition in rats are minimal, their interactions with a secondary hypothyroidism indicate that early underfed rats have clear physical alterations and similar deficits in the reflex activity, huddling response, motor development, self-grooming, swimming abilities, startle response and open field performance [34] [43] [44] [45] [46] [47].

Underfed central auditory alterations

Morphometric studies in the brainstem of normal adult rats have shown that the superior olivary complex have two pairs of bulbar nuclei located at each side of the midline, the lateral superior olivary nucleus (LSO) and the ventral medial trapezoid body nucleus (VMTB). Moreover, the olive cochlear bundle (OCB) consists of two modulatory systems of the auditory afferent signals from the cochlear organ, one crossed and the other ipsilaterally distributed on the basal portions of Corti organ hair cells [48] [49] [50]. Furthermore, studies using axonal retrograde transport (HRP) indicated that LSO unmyelinated axons connect ipsilaterally with the internal Corti hair cells already mature at birth to integrate signals of the internal ear related to tonal location; meanwhile the VMTB myelinated efferent innervate immature outer hair cells of the Corti began at birth to integrate sound frequencies, achieving maturity until PD 15 [51] [48] [49]. Neonatal undernutrition by separating pups (12 h) from the mother in an incubator at PDs 1 - 24 was associated with significant and consistent dendritic reductions in the VMTB with unstable effects in the LSO, as seen by Golgi-Cox staining. The data suggested that early undernutrition consistently interfered with the auditory signals generated at the outer hair cells by environmental auditory cues. The decrease in distal dendritic prolongations of these brain stem neurons to modulate the afferent auditory discharges of the outer hair cells via the OCB may be relevant in the integration of complex processes related to habituation and attention span, tonal discrimination, hearing protection and cognition of early underfed rats [6] [52]. Furthermore, other food restriction studies analyzing motor cortical pyramids restricted outer cochlear auditory stimulation by bilateral occlusion of the external ear channels from PDs 5 - 30. Golgi-Cox staining showed that motor pyramids at PDs 12, 20 and 30 exhibited significant reductions in the somatic area of the control occluded group versus the control group in the three ages; and the underfed occluded group versus the control group at PDs 12 and 20, reductions only occurred at PD 20; in the underfed occluded group versus the underfed group reductions only occurred at PD 20. Similar reductions in the somatic perimeter were obtained when comparing the control occluded and underfed occluded groups with their respective controls at PDs 12 and 20. Moreover, the total number of dendritic branches from the first to the fifth orders indicated consistent reductions mainly in the distal portions of dendrites in underfed occluded versus underfed groups; and underfed occluded versus control group at PDs 20 and 30 [6] [53]. In summary these findings confirm the noxious role of early food restriction and the external ear occlusion on the distal portions of the dendritic arbor measurements, at the cochlear and motor cortical pyramids during development. Furthermore, the anatomical alterations of large cortical pyramids could be relevant to understanding the disrupted motor activity integration, in the dynamic plasticity of human akinetic autism disorder [53] [54] [55].

Electrophysiological auditory alterations

The onset of the auditory function in rats, as analyzed by recording auditory nerve-brainstem evoked responses begins on PDs 12 - 14 by using air conduction with highly elevated thresholds and reaches maturation between PDs 12 - 16

[56]. Additionally, the development of auditory averaged evoked potentials recorded in the scalp of the normal rat by sound stimulation showed a mean peak latency of around 130 msec versus 195 msec in underfed subjects at PD 10. Moreover, the mean peak of the primary auditory component in controls gradually decreased to 30 msec in normal rats and delayed to 80 msec in underfed rats at PD 15. The latency of the repetitive secondary responses in controls was of 160 msec versus 170 msec in underfed rats at PD 10 and reduces gradually at 80 msec in controls versus 85 msec in underfed animals at PD 15 [36]. These measurements suggested that the prolonged latencies of the mean primary auditory responses in underfed rats may correlate with a poor axonal caliber spectrum and reduced myelination that slows down the conduction of the electrical responses [15] [38] [57]. The latency of the repetitive secondary responses at PD 10 was alike in both control and undernourished rats (35 msec). However, the duration of these responses was of 30 msec in controls and significantly sustained (45 msec) in underfed rats, suggesting a prolonged process of integration in the cortical auditory signals [36]. In this regard other studies suggest that the specific reticulo-thalamic ascending system is related with the first component of the rapid auditory cortical response, whereas the late repetitive secondary components depend on the nonspecific ascending auditory system projecting to the dendritic tree of layer V auditory cortex pyramids [14] [36] [58]. All together current findings suggest that pre-and neonatal undernutrition disturb the nonspecific system's development more than that of the specific ascending system, including the synaptic relays and axonal myelination of the central auditory cortex that interfere with the neuronal functional integration [14] [36] [59]. In this regard, suckling undernourished rats by separating the mother for a part of the day, and with restricted food intake until PD 60, showed a reduced proportion of myelinated corticospinal axons (34%) compared with controls (43%), and significant reductions in the myelin-specific galactolipids contents [59]. Additionally, in rats malnourished with an isocaloric low protein diet during the perinatal period (8%), the anterior part of the callosal interhemispheric system that connects the prefrontal cortices decrease in size at PDs 45 - 52 compared with that of control rats (25%), and without significant differences between the middle and posterior callosum parts [60]. Furthermore, in similar protein reduced malnourished rats, cortical spontaneous activity diminished, and prolonged latencies in the somatosensory evoked transcallosal responses to electrical stimulation at PD 13, without effects at PDs 60 - 66 underlying possible subcortical mechanisms [61]. In summary these findings were related to impaired callosal synaptic connections and/or reductions in the myelination of their fibers, which interfered with the interhemispheric nerve impulse transmission for integrative phenomena at the prefrontal cortex (PFC), which is indispensable for maternal retrieval of pups and attentional cognitive performance [24] [62] [63].

Another group of relevant electrophysiological alterations is associated with the effects of undernutrition on the auditory electrocorticogram (ECoG) maturation, compared with the sensorial integration in the frontal and occipital cortical regions. Gross observations of the ECoG of underfed rats by separating pups (12 h) from the mother and littermates (4 pups) into an incubator, showed when compared to controls a marked increase in the proportion of slow waves and a reduction in the voltage before PDs 16. By PD 18 the adult characteristic in both groups appeared. Furthermore, the average frequency measurements of the ECoG in starved rats indicated at PDs 5 - 30 a marked increase in the proportion of slow frequencies than controls attenuated until 30 days of age. In adult underfed rats statistically significant differences in the average frequency of the temporal cortical region showed a higher proportion of slow frequencies than frontal and occipital areas. Maturational changes elicited by early undernutrition may result in severe alterations of cortical synapses, the neuronal interactions, and in the membrane properties excitability of the temporal ECoG than frontal and occipital areas [64]. In summary the persistence of a higher proportion of slow frequencies of the temporal ECoG in adult rats with early food restriction, supports the view that the temporal lobe is particularly sensitive early in life to the deficiency of nutrients, and other associated risk factors interfering cognitive development.

Reticular thalamic nucleus alterations

In the rat the reticular thalamic nucleus (RTN) is located along the rostro lateral surface of the dorsal thalamus, segregated in its caudoventral area, and widely connected with the inferior colliculi, the adjacent thalamic sensory nuclei, and the auditory cortex to reciprocally modulate ascending-descending auditory information [65]. The RTN also receives in its rostral part a group of convergent afferent axons from the basal ganglia and motor cortex [66]. Because of its anatomical organization, the RTN has been associated with the appearance of complex cortical activity synchronization during the slow wave sleep and the waking state, by increasing the sensory information through the thalamocortical projections that energizes the PFC during the attentive state [67]. Although, little is known about the effects of early undernutrition on the neuronal RTN neuron development, a Golgi-Cox study in control and underfed rats by separating animals (12 h) at PDs 12, 20, and 30, showed a significant reduction in the cell area of 630 neurons in neonatally underfed rats, as well as a consistent significant reduction in the total mean number of dendritic prolongations per neuron in early underfed rats at all ages tested. Therefore, these findings are in line with the hypothesis that perinatal environmental influences may interfere with the maturational deficiencies of central thalamic modulatory mechanisms underlying sensory afferent transmission [68] [69] [70]. In the rat the thalamus as a grand central station relates to the inferior colliculi, an ancient ostensory structure that projects to the medial geniculate body and then to the auditory cortex. The inferior colliculi strongly connect with lower brainstem structures evolutionarily emerged from the touch, which underlie innate and emotional activities when compared with other sensory systems [71]. Additionally, the auditory system is a unique sensory channel with more axonal commissural connections at different brain levels, that widely spread neuronal information at each side of the brain

[72]. These ontogenetic origins of the neuronal auditory network may be relevant to understanding, why in humans the slow tempo music can evoke deep autonomic responses, such as crying, and tachycardia which could be helpful in music therapy and for the study of the temporal cortical substrate underlying musical integration [73] [74] [75]. In summary the sensorial afferent transmission in route to the specific cortical regions for its integration, at lower brain stem structures and the RTN is vulnerable to early food restriction that interferes with the sensory modulation of sensory signals.

Present findings support the hypothesis that early food restriction and stressful conditions associated to delayed sensory systems maturation, severely interfere with the limbic structures and the elaboration of cognitive processes. Briefly, the auditory ascending information from the periphery transmitted along a brain substrate affected in their organization and functions, which reaches the impaired temporal cortex of underfed subjects. Thereafter, the information expanded to the PFC, the anterior cingulate and motor cortices integrating descending influences on the lateral hypothalamus, the BLA, the brainstem and hippocampal structures underlying phonation and motoric behavioral cognition. In the case of humans, remain unknown how our memory experience stored in the temporal lobe and the hippocampus combined with cortical-subcortical emerging mechanisms generate, spatial learning, and attentional behaviors. However, the steps in the processes of auditory cognition remains poorly understood and require further investigation to provide relevant insights by using new methodological approaches.

Prefrontal cortical alterations

Over the past decades, studies have analyzed the impacts of neonatal undernutrition by transferring the same (n = 4) half of at least two litters from the nest to an incubator (12 h) from PDs 1 - 24, followed by a balanced diet until PD 30. Studies have also explored the effects of early food restriction on distal dendritic segments of layer III pyramids, somatic area measurements and the number of spines of the dorsolateral prefrontal cortex (dPFC) neurons (rapid-Golgi) at PDs 12, 20 and 30. In underfed subjects, the distal dendritic arbors exhibited consistent hypoplasia, chiefly at PD 30, with reduced neuronal somatic, perimeter. and spine densities on basilar dendrites on all experimental days. These findings may interfere with the synaptic activity of the distal portions occurring at the dPFC, and cognitive performance in adulthood [9]. Furthermore, functional neuronal c-Fos reactivity of the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) were also measured in perinatally food restricted dams from G6 to G19 (50% to 30% of the diet), followed by a balanced diet from G20 to G21. After birth, pups were food restricted by rotating (every 12 h, PDs 1 - 24) two lactating mothers, one with her tied nipples. After weaning (PD 25), rats had an *ad libitum* diet. The maternal response at PD 90, and early underfed dams' motivation, taken as a cognitive response (retrieving, handling shavings and crouching), every 10 min at PDs 4 and 12, when the motivation of dams for pups was high or declining, respectively. The maternal motivation evaluated by immunostaining the neurons of the mPFC and the BLA after the removal of pups from the dams 90 min after suckling. Early underfed dams showed significantly reduced retrieval, shaving handling and crouching frequencies, as well as prolonged latencies for pup retrieval and for handling shavings, and crouching frequencies, as well as prolonged latencies for pup retrieval, and for handling shavings, and crouching. Additionally, underfed dams had Fos-I neuron deficiencies in the PFC, with little effects on the BLA. These findings suggested suboptimal sensory pups' activity to evoke maternal motivation and/or deficient maternal network electrical transmission that may be relevant for triggering deficient cognitive mother-litter bonds [9]). Current findings are in line with the role of the PFC in the integration of the sensory signals transmitted from different neuronal routes, including auditory signals with the limbic system structures regulating the internal emotional states, and cognitive spatiotemporal performance, such as, the maternal response, play behavior, attentiveness, and locomotion where the BLA plays an important role in maternal memory consolidation and conditioned learning [9] [67] [76] [77] [78] [79].

Additionally, the electrophysiological evoked responses to monaural noise exposure (120 dB sound pressure level, 1 h) recorded from the auditory cortex of an awake adult early underfed rats before and after acoustic overstimulation showed increased hearing threshold and transient enhancement (4 h) compared with the non-exposed ear [80]. Similarly, in adult rats the exposure to noise damage during early auditory development (125 dB SLP 8 min, at PD 14) disrupted the intensity perception and frequency discrimination of the auditory function [81]. Comparable results are known in the anatomical somatosensory cortex of adult monkeys and rats exposed to different forepaw tactile experiences. Thus, tactile impoverishment of rat forepaw exploratory movements for 7 or 15 days at PDs 80 to 115 after weaning, resulted in significant reduction of the size of the somatosensorial forepaw cortical representation, while environmental enrichment in tactile stimuli provoked the opposite effects in the cutaneous forepaw cortical representation [82]. In summary, the findings are in line with studies on the anatomical and functional developmental neuroplasticity, underlying neuronal networks activities in both normal and cognitive disrupted environmental influences.

Hippocampal deficits

The hippocampus is another brain structure that is necessary for spatial learning, memory and attentive behavior and is sensitive to the noxious effects of food restriction. Adult rats undernourished prenatally and during suckling evaluated in an 8-arm and then, a 16-arm radial maze. Underfed subjects showed significantly more error distributions in the complex maze, and in the time taken to make the choices in exploratory behavior than controls. These deficiencies were associated with alterations of hippocampal anatomical growth [83]. Additionally, in 2-month-old rats fed with a low protein diet (8% casein) for 6, 12 and 18 months compared with age-matched control and recovery rats, nourished first with a low protein diet (8% casein) and then a normal diet for 6 months. The total number of granule hilar, CA1 and CA3 pyramids decreased in malnourished rats including the food recovery group. Data showed a deficit in the number of neurons in the hippocampal area, associated with the behavioral process's alterations related to early food restriction [84] [85]. Additionally, early undernourished adult subjects exhibited impaired high-frequency electrical stimulation of hippocampal dentate granule cells to produce long-term potentiation compared to their controls, suggesting a clear dysfunction associated to food intake in the adult hippocampal activities [86] [87].

In morphometric studies comparing a low protein diet fed group (8%) and its respective control (24% balanced diet), the hippocampal granule cells of the fascia dentata, showed significant reductions in cell somatic, number of spines, and dendritic extent. Moreover, dendritic branching complexity in the outer molecular layer appeared from PD 15 until PD 220. Furthermore, the dendritic arbor deficits associated with prenatal protein malnutrition occurred at PD 30, while synaptic spine density appeared until PD 90, suggesting a delayed period of synaptic connectivity related with other factors such as the impact of environmental sensory stimuli to promote spine development and attentional cognition [67] [87]. In summary early malnutrition negatively influences differently the hippocampal growth and its functions, as a significant structure associated with the neuronal plasticity underlying adulthood cognition.

Amygdala deficiencies

The behavioral alterations associated with early undernutrition or malnutrition are consistently linked to abnormal emotional responses, and have been described as locomotor hyperactivity, aggressiveness, increased urination, defecation, and low exploratory activity in the open field [88] [89] [90]. Moreover, when early underfed rats are exposed to novel environments or to stressful conditions, they have higher blood pressure, and elevated serum corticosteroids values [91]. Furthermore, suprathreshold electrical stimulation of the amygdala was necessary to elicited kindled motor seizures, in early malnourished rats compared to controls, suggesting reduced excitability of this structure to provoke epileptic discharges [61]. One morphometric Golgi-Cox study examined the BLA, central (CEA) and medial (MA) nuclei of the amygdala in early underfed subjects (separating pups daily, 12 h) of the same half of litter (n = 4) in an incubator from PDs 1 - 23. On PDs 12, 20 and 40, eight pups of each condition, and 150 neurons per nucleus examined. Neurons taken from underfed rats at the three amygdala nuclei showed reduced somatic and dendritic field areas compared to controls on PDs 12 and 20, with no effects at PD 40. Moreover, neurons from BLA and CEA showed a reduced number of dendrites with minor effects in the MA neuronal somatic. These findings suggest that the nuclei have different degrees of vulnerability to neonatal food restriction, related to their functional cognitive activity [92]. Furthermore, the neuronal c-Fos reactivity of the mPFC and BLA evaluated in early underfed F1 dams for maternal motivation (retrieving pups, handling shavings and crouching measurements) at PDs 4 and 12 of lactation. Underfed dams showed lower frequencies and prolonged latencies in pup motivation, associated with Fos-I neuronal deficiencies in the PFC, with minor effects on the BLA possibly because the reduced stimuli of the pups or poor network responsivity [9]. Another possibility is that the BLA may play a role in the maternal memory consolidation and provides pup-related sensory inputs to maternal brain structures which potentiate the ability of BLA neurons to stimulate goal-directed maternal responses [77] [78] [93]. In this regard it is relevant that several cognitive responses need a cortical amplification of the sensory stimuli reaching the cortical representation areas to organize and elaborate adaptive cognitive responses. Thus, the optogenetic stimulation of the BLA through a circuit connected with the RTN inhibits the cortical spontaneous responses, but not the enhanced tone-evoked activity recorded in the thalamic medial geniculate body and the auditory cortex of the rat to potentiate relevant environmental information for the elaboration of complex functional responses [94]. Briefly, the mPFC, and the BLA related to with the lateral hypothalamus (LHA) to maintain a balance for the control of complex cognitive motivated behaviors.

Cingulate cortex alterations

Basic morpho-functional studies indicate that the anterior and posterior cingulate cortices receive information from the orbitofrontal, dorsolateral and parietal cortical areas in association with other limbic structures, including the hippocampal memory system to integrate action outcomes such as visuospatial information, attention, emotion, memory, learning and maternal retrieval that are functionally disorganized when some part of their neuronal networks are affected [17] [24] [62] [95] [96] [97]. In this context perinatal protein malnutrition impairs a sustained attention task with a randomly applied distractor. This task evaluated using radiolabeled 2-deoxyglucose as a functional marker in the PFC of adult rats. Based on previous studies the authors suggest a fundamental role of the hippocampus in the malnourished rats, in a function integrated at the PFC [67]. Additionally, the neuronal pathways related to the demands of attention run from the ventral tegmental area projecting to the medial forebrain bundle and lateral hypothalamus, the accumbent nucleus, and the mPFC via the mesolimbic and neocortical dopamine pathways that energize the cortical regions that focus on immediate emotional needs associated to early undernutrition [24].

3. Mother-Litter Bonds and Hearing Cognition

Neuroanatomical studies by using a single or a double retrograde tracer technique to map the connections between the mPFC, BLA, and the lateral hypothalamus (LHA), have established a highly interconnected network essential for cognitive processes, such as learning, attentional, and decision-making activities [98]. Moreover, the mPFC and the BLA strongly connect with the lateral hypothalamus (LHA) in a parallel balance mechanism for the control of feeding and other motivated behaviors including the maternal care [17]. Thus, the descending activity from the LHA to the brainstem structures modulate the activation of the caudal nucleus ambiguous (AMBc) [11] [99].

In mammals, the mother-litter bonds play a fundamental role in species preservation by eliciting plastic brain changes in the mother, to produce maternal behavior adaptive mechanisms directed to the newborn for their survival and brain development [11] [99]. In this context, rat pups emit ultrasonic vocalizations (USV) that serve as powerful communication mechanisms with the mother. These vocalizations have been studied in several distress and motivational situations, such as separation from the dam (frequency range from 30 to 50 KZ) and exposure of newborns to cold, acute isolation, and pain cues at 22 KZ, [1] [2] [99] [100]. Furthermore, the characteristics of these USV altered by perinatal malnutrition, associated with the damage of various structures of the central nervous system [7]. From other studies, it is known that the brain stem areas associated with swallowing, breathing, and laryngeal motor innervations, are necessary for phonation [101] [102]. Neuroanatomical tracing studies provide a description of the central brainstem connections of the axons within the superior and recurrent laryngeal nerves, the latter with a special motor innervation to the intrinsic laryngeal muscles arising from the AMBc motoneurons [103] [104]. These muscles and vocal cords morphology changed into postnatally underfed rat pups [105]. Experimental data indicate that pup USVs motivate the dam in association with olfactory, visual, and auditory stimuli to localize, retrieve and protect the young in a safe nest environment [7]. Additionally, rats with deficient protein diet (6%) for 5 weeks prior mating and during pregnancy exposed to a brief period of isolation and cooling (20˚C) at PDs 7, 9, and 11. USVs emitted by their pups compared with those of controls (25%). Twelve distinct types of calls analyzed according to their sonographic patterns. At PD 7, the mean peak sound frequency (irrespective of call type) was significantly higher, and constant frequency calls were of both higher frequency and longer duration. At PD 9 malnourished rats emitted smaller variety of calls, with significantly fewer ascending USV, while at PD 11, they produced greater ascending frequency calls [7].

These USV alterations in response to specific underfed insults reflect disruptions occurring in the dendritic branches, perikaryal measurements and the salutary effects of massage stimulation along the brain auditory relays, and the brainstem motor AMBc related to the innervation of the laryngeal intrinsic muscles underlying specific altered phonation [106]. The findings of altered emission of ascending or descending USVs in malnourished or undernourished pups are concurrent with reduced maternal anogenital and fur-licking of the pups, and newborn learning associated with the mother, the reduced ven trum somatosensory contacts provided to the pups, and less nursing time spent with the litter, which impacts the milk secretion and care of the pups. The deficient mother-litter bond also hinders newborn brain maturation, behavioral performance, and the response to stress, all of which have been associated with brain disorders and cognitive deficiencies in adulthood [96] [107] [108] [109]. Unfortunately, the specific dialog (*i.e.*, USVs) between the dam and her litter when faced with uncomfortable environmental situations is unknown. Furthermore, USVs reflect the close neuronal deficiencies in connectivity between the sensory information including the auditory system, with the ancient limbic structures to maintain early basic physiological needs [96] [109]. In summary, deficiencies in the maturation of the olfactory, gustatory, visual, somatosensory, and auditory systems of newborns commonly seen in early food restriction, severely disrupt the sensory communication with the dam to achieve early experience for the progeny development [7] [30] [31] [110]-[115]. Deficient mother-litter bonds also affect the young's brain growth, behavioral development, and stress responses all of which have been associated with mental disorders at later ages [113].

4. Conclusions

The current findings showed global morpho-functional auditory impairments associated with perinatal undernutrition or malnutrition, resulting in relevant risk factors for brain anatomical organization and functional development in the adult rat. Furthermore, this experimental evidence provides consistent information that may be helpful to understand the long-term disruptions in the auditory cognition of early underfed humans. The main peripheral and central auditory functional alterations related to early food restriction, also depend on concurrent risk factors, including deficient brain morphogenetic hormones and growth factors. Moreover, the increased stress glucocorticoids impair sensory integration, memory store, and limbic neuronal activity subserving emotional and cognitive performance.

Furthermore, mother-litter bond deficiencies associated with perinatal food restriction during suckling, sensory deprivation, exposure to stressful unfamiliar conditions, and the impaired early learning experience, among other poorly understood factors, may interfere with the synaptic connectivity, the integration, and emerging long-term auditory cognitive processes at later ages. The current findings also provide evidence that the impaired auditory cognitive development concurrent with perinatal food restriction may be related to non-adaptive emotional responses. However, further studies to identify effects using the same or different underfeeding procedures at developmental ages, as well as to understand the role of other sensory systems, and analyze morphometric and image procedures of limbic structures underlying auditory cognitive phenomena will be necessary.

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Conflicts of Interest

The authors declare no conflict of interest regarding this work.

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