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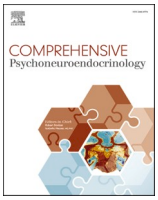

Multi-level hypothalamic neuromodulation of self-regulation and cognition in preterm infants: Towards a control systems model

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ABSTRACT

Preterm infants, age-corrected for prematurity, score on average, 10 points lower on IQ tests than full-term infants tested at comparable ages. This review focuses on the potential contribution of the hypothalamus to cognitive neuro-regulatory development in preterm infants through its bidirectional neural connections with the prefrontal cortex and its neuroendocrine activity. It aims to clarify the central role of the hypothalamus in preterm high stress situations and in influencing cognitive development via its connectivity to the cerebral cortex. The review further evaluates epigenomic sensitivity to environmental inputs. Recent results suggest that an optimal range of DNA methylations (via a continuous process of decreasing levels of receptor methylations that are too high, and increasing levels that are too low) appears necessary in order to reach an adaptive level of receptor availability. Several studies have demonstrated amelioration of preterm infants' stress while in the Newborn Intensive Care Unit (NICUs) and following discharge. The authors postulate that feedback mechanisms and correction signals are the basis for a hypothalamic homeostatic modulating function, a "hypothalamic resistance response", which may account for the stress reduction brought about by in- and post-NICU early interventions and their results of promoting self-regulation and cognition.

1. Introduction

A seminal meta-analysis [17] shows that infants born too early and age-corrected for their prematurity scored on the average ten IQ points lower than age-equivalent full term born children. Studies continue to confirm the risk for cognitive performance in premature birth, e.g., in school-aged children born preterm, on the following scores from the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV):, verbal comprehension, perceptual (non-verbal) reasoning, working memory (WM), and the full-scale intelligence quotient (FSIQ) [39] and in young adults on the Verbal Intelligence Quotient, Performance Intelligence Quotient and Total Intelligence Quotient of the Wechsler Adult Intelligence Scale - Revised (WAIS-R) [108]. A recent meta-analysis [91] evaluated a number of specific cognitive skills at school age and provided evidence that preterm birth is associated with academic underperformance in aggregate measures of reading and mathematics, as well as a variety of related subskills. A sample of 89 children born at mean gestational age 29.9 weeks (mean birth weight 1235g) and tested at five years corrected age as a group showed IQ scores at the mean of the test (97.8 ± 12.7), yet a disproportionately higher number than the expected 16%, namely 21.3%, scored below 85, i.e., one standard deviation below the mean, and 2.2% additionally showed cerebral palsy [43]. At younger ages very preterm infants on average scored below 70 on both the mental and psycho-motor developmental scales of the Bayley [58], which signifies severe cognitive, self-regulatory and motor system impairment [19]. Utilizing the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [55] others reported composite scores in the cognitive, self-regulation, language and motor domains of 95, 89 and 94, respectively for very preterm infants. Neurodevelopmental impairment was present in 20% of the children, with 5–18% exhibiting significant delay in either cognitive, self-regulation, language or motor domains, seven (4%) children had cerebral palsy,

Abbreviations: Newborn intensive care unit, (NICU); Prefrontal cortex, (PFC); Magnetic resonance imaging, (MRI); Hypothalamic pituitary adrenal axis, (HPA axis); Lateral hypothalamus, (LH); Corticotropin-releasing hormone, (CRH); Oxytocin, (OT); Hypothalamic pituitary thyroid axis, (HPT axis); Hypothalamic pituitary gonadal axis, (HPG axis); Controlled process variable, (CPV); Set point, (SP).

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and three (2%) were deaf [1].

Self-regulation in the NICU and in the first months after discharge is assessed by several measures, including changes in heart rate, irritability and difficulty with routines [27,85], gaze, gaze-aversion and self-soothing behaviors (thumb-sucking and playing with clothing) in stressful situations [60] and at 18–21 months by competency with sleeping, eating, sensory sensitivity, and negative emotions [32] and confirmed compromised levels on these measues. Thus, the research results suggest that very early born preterm infants are at risk for difficulties in cognitive and self-regulatory function. Research has yet to provide a clear understanding of the potential mechanisms that might underlie these deficits. Nevertheless, we note that a large proportion of infants/children develop typically following preterm birth especially if no brain injury incidents are involved. In this review we suggest that hypothalamic pathways might underlie the development of self-regulation and cognitive difficulties in preterm infants.

The hypothalamus is a regulatory center for many brain functions. It receives and transmits information from and to a large number of other brain regions. It is commonly agreed that early stress in the Newborn Intensive Care Unit (NICU) environment affects cognitive and self-regulation development of preterm infants [5,32]. The hypothalamus appears to play an important role in early neurobehavioral development through its involvement in the developing stress reaction of the preterm infant and bidirectional connections with prefrontal cortex (PFC), the locus of control of cognitive and self-regulation capacities as well as executive functions [117].

A theoretical model is proposed for homeostatic developmental control focused on the hypothalamus in its interaction with the frontal lobes and specifically prefrontal cortex. The model implies that immature hypothalamic signaling is a second-by-second process that leads to progressive infant reactivity in given conditions or situations. The Synactive Theory [3] of neurobehavioral development is in keeping with the suggestion that preterm-born infants likely evaluate environmental conditions and stimuli through their as yet immature hypothalamic regulation filters, which in turn have deleterious effects of hyper-arousal and agitation. Yet in conditions of behaviorally calming interventions, such over-reactivity is dialed down and in turn leads to more modulated, increasingly more mature behavioral and likely improved hypothalamic regulatory control. This, it is postulated, will have profound effects over time for improving the overall neurodevelopmental and specifically cognitive and self-regulation competence of infants born preterm.

The aims of this review are (1) to outline an integrative view of hypothalamic control of early behavior from neurobehavioral, biochemical, endocrine and epigenetic perspectives; (2) to evaluate the role of effective interventions in hypothesized hypothalamic adaptive control and (3) to suggest a theoretical control systems model based on this integrative view.

2. Early life stress, the hypothalamic-pitutary-adrenal (HPA) axis, cognitive and self-regulation development

Early experience can shape later developing sense of control and predictability essential for self-regulation [15]. NICU environments support preterm infants' survival, yet also confront the infants with many adverse stimuli and limit maternal proximity [30]. Stressful, adverse unexpected stimuli include bright light, loud sounds, many painful medical interventions at unpredictable times, lack of parental touch, isolation in the incubator, and lack of opportunities for self-soothing and -regulation as well as being soothed and regulated by others [120]. Thus, for preterm infants, stress is inevitable. This means that preterm infants show altered programming of the hypothalamic-pituitary-adrenal (HPA) axis involved in the developing stress reaction, from early stages of development onwards [24,111].

Early life stress before full-term equivalent age is a risk factor for long-term deleterious effects on cognitive and self-regulation development due to disruption of *in utero* homeostasis. The impact of stress during this early period is evident not only in the HPA axis itself but also in the amygdala, the hippocampus and in frontal and prefrontal cortex (PFC), the areas that are connected with hypothalamic regulation of the HPA axis [13,87]. Additionally, high glucocorticoid levels, regulated by the hypothalamus, also are associated with impaired cognitive and overall neuro-development. For example, basal cortisol at 15 months of age corrected for prematurity was reported to be inversely correlated with infant cognitive development (assessed by the Mental Development Index of the Bayley Scales of Infant Development) after adjusting for psychosocial parameters and obstetric risk [51]. This provides further evidence that HPA axis activity in infancy modulates cognition. In addition, it has been noted that flaccid states and low levels of crying and protest in high-risk preterm infants are common [7], suggesting low levels of stress-regulation, which is mediated by cortisol, among other factors.

Increase in glucocorticoids during chronic or intense stress also results in deficiencies in frontal and prefrontal cortical function [86,87]. Corticotropin releasing hormone (CRH) connects to two types of receptors, CRH1, which mediates acute stress reactions via the activation of the HPA axis, and CRH2, which is part of the post-stress recovery and reduction of the HPA activity [63]. Both of these receptors are present in brain structures that are involved in stress reactivity, including the central amygdala and PFC. This is relevant as emotional reactivity, stress and fear interfere with cognitive, self-regulation and executive function. We note that frontal, and especially PFC, are responsible for executive functions, including working memory, flexible thinking, mental and emotional control, decision making and related integrative regulatory and mental functions of complex information analysis and synthesis [5,79].

Animal models suggest that activity of the stress-responsive HPA axis and its corticoid receptors are involved in the effects of stress not only in the infant but also in the mother or other caregiver, and in turn may mutually potentiate one another [41,63]. A hyper-responsive HPA axis may have been beneficial for self-protection and survival in early human evolution due to the advantages of hyper-vigilance. Now however it produces increased cost and heightened vulnerability for human neurodevelopment [117].

Moreover, relative adrenal insufficiency characterizes the preterm infant born before 32 weeks gestational age. Preterm newborns lack the capacity to generate a full adrenocortical response to stress or illness [52], which conversely, turns to a disproportionate increase in glucocorticoid action later in development. Thus, preterm born infants show deficiencies along multiple aspects of the HPA axis, such as in over-reactivity of the hypothalamus, poor pituitary responsiveness to exogenous CRH and reduced activity of 11β-hydroxylase, an enzyme needed for cortisol synthesis [52]. Very preterm infants have further been shown to have attenuated HPA axis reactivity to physical and socio-emotional stress later in life [56,113] and a different (from term born infants) salivary cortisol regulation pattern in response to a stressful "still-face" procedure [112]. Furthermore, when examining mother-infant co-regulation of the HPA-axis (a topic in which inconsistencies have been found in the literature), dyads of very preterm infants and their mothers were found to be less able to adapt reciprocally and dynamically to stressful conditions, compared to dyads with full term infants [112]. Thus, the activity/reactivity of the HPA axis appears to be abnormal in preterm-born infants. To date, some long-term hormonal effects have been identified. For example, increased basal cortisol secretion rates and adrenal hyperandrogenism in very preterm born girls, later in life, are partially expressed phenotypically [52]. Furthermore, at age 23 years, preterm birth with neurological complications resulted in higher cortisol reactivity to social evaluative threat compared to full-term, small for gestation age, medically ill, or healthy preterm controls [128].

Many very preterm (i.e., <32 weeks of gestation) infants do not generate an adequate adrenocortical response to stress or illness and show adrenal insufficiency [52]. At later stages of development such

infants show elevated glucocorticoid reactivity. Accordingly, infants with greater sensitivity to glucocorticoids (carriers of a glucocorticoid receptor polymorphism) showed poorer cognitive and self-regulation scores in late adolescence [52]. Preterm infants at three months corrected age have been observed to have lower cortisol levels than full-term infants, whereas at eight months they showed higher cortisol levels than full-term controls [57]. Although there are several reports of attenuated (hypo-response) reactivity of the HPA axis of very preterm infants to pain stimuli such as during vaccination, other studies show hyper-responsivity or prolonged cortisol elevations [92]. Taken together the data show that very preterm newborns show deficiencies in many components of the HPA axis, however the pattern of this may differ under different baseline and stressful conditions. The inconsistencies in the literature regarding hypo- and hyper-reactivity of the HPA axis may represent two extreme conditions of dysregulated stress reactivity in preterm infants: The over arousal states leading to higher-than-expected heart rate (tachycardia) vs. the flaccid and hypotonic conditions (bradycardia) leading even to apneas and low oxygen saturation [6,70].

Regarding long term effects of prematurity, cortisol levels have further been found to be associated with long-term neurocognitive effects in children born prematurely in comparison to their full-term controls when tested at seven years corrected age. The children's cortisol response during testing on the study day were associated negatively with attention problems, and positively with thought problems [20]. Of note is that preterm infants experience a much shorter time in the supportive *in utero* environment than their full-term peers. Thus, they lack the protective role of cortisol in late gestation [38]. The investigation of cortisol's negative and protective roles in preterm infants is a continued active research focus [38,111]. These findings suggest long-term effects of hypothalamic complex early programming in children born prematurely. Specifically, as outlined below, the developing hypothalamic complex is suggested as a crucial factor for neurocognitive development in preterm infants even beyond the role of its HPA axis.

3. Hypothalamic axes, the crosstalk between them and cognitive, self-regulatory development

Recent studies highlight the interest in the preterm infant's hypothalamus and its three axes, the HPA, hypothalamic pituitary thyroid (HPT) and hypothalamic pituitary gonadal (HPG) axes. It is noted, as detailed below, that the role of the HPT and the HPG in preterm infants have distinct patterns of impacts on cognition and self-regulation as well as interrelated modes by their crosstalk with the HPA.

3.1. The hypothalamic pituitary thyroid (HPT) axis

Congenital hypothyroidism is the most preventable risk factor for intellectual disability. Maternal hypothyroxinemia, common during pregnancy and lactation, has been reported widely in preclinical and clinical studies to interfere with cognitive and self-regulation development [94]. Thyroid dysfunction is reported in many preterm born infants and marked dysfunction has been reported in those born at extremely early gestational ages [93] or with intra-uterine growth restriction [116]. Thyroid hormone levels were found to be lower in correlation with earlier gestational age at birth and during NICU hospitalization and with severity of illness [31,106].

Hypothyroidism *in utero* may lead to fetal brain damage and is closely related to neurodevelopmental deficiencies. Fetal brain development in this condition was found to be altered on the axonal, dendritic and synaptic levels [94]. Supplement of iodides was shown to be ineffective at ameliorating neurobehavioral functioning [142]. On the metabolic level, thyroid hormone is a crucial component of the cellular fetal-mother interaction during pregnancy. It also plays a fundamental role in the metabolic changes during transition to the *extra-uterine* environment including effects on respiration and cardiac functions [116]. It has been suggested that the underlying mechanism for hypothyroidism in preterm infants involves inadequate functioning of the HPA axis, implying lower cortisol levels compared to those required for the appropriate transition to the *extra-uterine* environment. This highlights the reciprocal impact between the axes. Cortisol plays a crucial role in the transition to the *extra-uterine* environment [61].

Fetal cortisol levels increase significantly from the 30th week of gestation, increasing about five-fold during labor at term. This increase supports the cardiovascular, cardiopulmonary, endocrine, and thermoregulatory aspects of the transition. In premature delivery, the levels of cortisol may be insufficient for optimal transition [62]. In this respect, adrenal immaturity in preterm infants is associated with lower cortisol rise at birth, further complicating transition [138] and often producing hypotension which can be treated with exogenous cortisol administration [48,98]. In addition, metabolic stress and reduced mechanisms for coping with *extra-uterine* environmental stress also have been related to reduced levels of thyroid hormone in preterm infants [93].

Given the association reported between hypothyroidism and intellectual disability, it is suggested that preterm infants are equipped poorly for managing adequate HPA stress regulation, a condition which may be involved in further compromising their HPT function and stress reactivity. Preterm infants' deprivation of late stage cellular fetal-mother interaction during the missed last trimester of pregnancy due to early birth likely adds to preterm infants' hypothyroidism and thyroid hormone reduction in the first weeks *postpartum* in preterm infants. Hypothyroidism, in turn, may be involved in the association found between lower gestational age at birth and impaired cognitive and self-regulation functioning (assessed by increases in externalizing and internalizing behaviors and risk for developing ADHD) at later development [17,91].

3.2. The hypothalamic pituitary gonadal (HPG) axis

Important and significant differences in levels of the pituitary-ovarian hormones were found between preterm-born girls and full-term-born controls [11]. In addition, it has been shown that circadian rhythms of gonadal hormones are required for the cessation of the stress response through the HPA axis [105]. Moreover, fluctuations of progesterone and estrogen are relevant for females' optimal HPA axis reactivity. In males, early programing of the testosterone effects on the HPA axis and its reprogramming during puberty are necessary for such adaptive HPA axis reactivity in adulthood [105].

Thus, all three axes of the hypothalamus are relevant to the understanding of prematurity and its resulting compromised cognitive and self-regulation development by direct or secondary impact.

3.3. Crosstalk between the HPA, HPT and HPG axes

Crosstalk between these three hormonal axes of the hypothalamus has been reported at the methylation level. Decreased DNA methylation of the glucocorticoid receptor gene (NR3C1) has been reported to be associated with increased binding of transcription factors involved in the stress response to compensate for the low cortisol levels and low regulatory capacity of preterm infants in coping with *extra-uterine* stress conditions. This further implicates the significant role of the hypothalamus in the development of preterm infants [54]. The adequacy of the HPG axis crosstalk with the HPA axis may lead to adaptation vs. deficiency respectively in terms of stress reactivity during later development. The reactivity of the HPA axis ceases due to the inhibitory function of adrenal glucocorticoids [105].

The effects of thyroid hormone levels, shown to be reduced markedly in preterm infants, on the promoter region of the gene responsible for release of Gonadotropin Inhibitory Hormone (GnIH), may lead to alterations in the onset of puberty. Thus, thyroid hormone deficiency may have long-term significant effects on the later development of preterm infants [130]. In addition, Type 3 iodothyronine deiodinase (DIO3)

enzyme, which regulates the T3 effects on thyroid receptor binding, is known to be sensitive to environmental inputs including effects of stressful conditions, such as the NICU environment, mediated by the HPA axis at a neurobehavioral outcomes level [59]. The direct and indirect effects of the three hypothalamic axes, HPA, HPT and HPG, at a DNA methylation level (as described below) as well as the feedback loops between the axes and the central regulatory function of the hypothalamus, all impact preterm infants' development, while exogenous stressors during *extra-uterine* life remain ever-present additional sources for compromise.

3.4. Hypothalamic neurohormonal development

3.5.1. Hypothalamic neurohormonal activity, self-regulation and cognitive development

Three hormones, namely Oxytocin (OT), Cortisol and Melatonin, are postulated to be among the most relevant for the NICU experience of the preterm infant. OT mediates mutual parent-infant modulation of neurobehavioral activity through affectionate touch, which is associated with enhanced bonding with the parent [132,134], the infant's primary co-regulator throughout childhood [2]; cortisol is a regulator of stress reactivity; and Melatonin plays a role in the maturation of circadian rhythms and in turn has been shown to influence Bayley Scale [58]-measured developmental indices in preterm infants [44]. These neuroendocrine processes show the crucial role of the hypothalamus and hypothalamic modulation for the development of cognitive and self-regulation functioning in preterm infants.

Oxytocin (OT), the "love hormone" a specifically mammalian hormone, is released from the posterior pituitary and regulated by the hypothalamus via hypothalamic posterior pituitary neuronal connections. It is a naturally produced neuropeptide with nine amino acids. Oxytocin receptors (OXTR) are located in many brain regions and are differentially dense in frontal and prefrontal cortex. In fetal development diurnal maternal OT secretion is protective of fetal brain development. Oxytocin is also released in the full-term newborn infant through gentle sensory stimulation, especially through soothing affectionate touch, such as being held skin to skin, and being caressed. Furthermore, intake of pleasant tasting food promotes OT release [80]. In addition, oxytocin regulates melatonin production [125] and melatonin and cortisol rhythms in turn are coupled inversely [28]. The direct and interrelated impacts of these neuroendocrine processes are suggested here as the core of the preterm infant's struggle to develop in the NICU environment which in turn has been shown to encompass long term implications later during childhood.

In contrast to term-born infants, preterm infants experience vastly different oxytocin exposures as they develop outside of the womb in demanding NICU environments [8], where soothing touch and pleasant food intake are rare. Their own endogenous oxytocin release, thus, is hampered significantly. This combination of factors affects hypothalamic OT regulation and OT protection for preterm infants and in turn is bound to affect their cognitive and self-regulation development [21].

Cortisol, the "stress hormone", regulated by the HPA axis, also has been found to be involved in the development of cognitive and self-regulation functioning. The establishment of circadian salivary cortisol rhythms is related to gestational age rather than to postnatal age. In 12 months old full-term-born children, elevated levels of maternal cortisol late in gestation were found to be associated with accelerated cognitive and self-regulation development as shown by higher scores on the Bayley Scales of Infant Development [55,58] while the opposite effect was associated with exposure to high levels of cortisol early in pregnancy [38]. Overall the research on associations between prenatal maternal cortisol and infant outcomes still requires strengthening [144]. Infants born prematurely fail to benefit from the late pregnancy contribution and protection of maternal cortisol. Exposure to elevated concentrations of cortisol early in gestation was found to be associated with a slower rate of development over the first year and lower mental developmental scores at 12 months corrected age [38]. A circadian rhythm of cortisol in preterm-born infants is established only by one month corrected age. Stressful environments and lack of maternal modulation appear to interfere with its establishment in preterm infants [67].

Melatonin, the "sleep hormone", is released by the pineal gland [74]. The pineal gland receives neural inputs from both central brain sites, including the paraventricular (PVN) and lateral hypothalamic nuclei and from hypothalamic sites starting from the suprachiasmatic nucleus (SCN) to PVN to intermediolateral nucleus in the spinal cord. From there, projections to the superior cervical ganglion connect to sympathetic neurons that project to the pineal gland [42,95]. Therefore, the hypothalamus regulates the function of the pineal gland and therewith of melatonin. The SCN of the hypothalamus is the primary regulator of circadian rhythms. These hypothalamic supra-chiasmatic nucleus cells and their afferent and efferent pathways emerge in humans around mid-gestation and on the average complete development at 18 months post full-term age [64]. Fetal rhythms during pregnancy correspond to the mother's external circadian rhythm as influenced by her hormonal activity and her exposure to environmental light-dark cycles [12]. Maternal melatonin decreases at exposure to white light, i.e., the complete mixture of all wavelengths of the visible spectrum. With birth, the human newborn loses the coordinating signals produced by the mother. Blood and urine melatonin cyclicity in the human infant are detectable by eight to nine weeks [71,74] and are well established by twelve weeks after term birth [124]. In term infants, melatonin is affected by environmental stimuli, including bedtime routines [44,47]. In preterm infants, understandably, delayed and disrupted melatonin production and maturation of diurnal rhythms have been reported due to constant exposure to white light in NICUs and discontinuation of the maternal melatonin regulation upon preterm birth [45,74]. In the preterm infant melatonin matures in parallel with the maturation of quiet sleep, which in turn is dependent on the infant's environment. Preterm infants' melatonin levels in the post term period were found to be lower than those in term born infants [18]. Furthermore they were associated with postnatal (2-weeks post-term) self-regulation scores (assessed by the Assessment of Preterm Infants' Behavior (APIB)) and later (9-months of age) cognitive (measured by the Mental Developmental Index of the Bayley scales) scores [44]. As quiet sleep periods in the full-term infant lengthen, i.e. mature with time, so does their maturation of melatonin production [44,47]. In preterm infants, sleep maturation is delayed as is their own melatonin production and maturation. Full-term infants' sleep begins with periods of *tracé alternant*, the repetitive bursts of high-voltage slow wave electrical activity alternating with attenuated 3 Hz mixed-frequency activity and active or rapid eye movement sleep, from which quiet sleep periods gradually develop [65,100,121]. Quiet sleep becomes progressively longer in interaction with environmental light-dark cycle and other environmental cues. Sleep development matures around 12 weeks after birth in healthy full-term newborns at which point quiet sleep is the first phase the infant enters before further on in the sleep cycle moving into active or rapid eye movement sleep [44,47]. These processes are delayed in preterm infants [33]. Of note is also that the maturation of quiet sleep is directly linked to the development of quiet alert periods [33]. In the preterm infant, the prolonged predominance of active sleep after birth is reduced only gradually. Preterm infants experience difficulties in entering into and maintaining a quiet sleep and a quiet alert state, which requires modulation of stress reactivity, a quiet, stable motor system and the capacity for higher heart rate variability. The quiet sleep and alert states are essential for cognitive and self-regulation development [14].

Aside from its response to light, melatonin also is known as an antioxidant and scavenger of free radicals and thus, is involved in optimal vs. compromised oxygenation [37]. In the preterm infant, melatonin development disruption leading to compromised oxygenation may interfere with frontal lobe development and therewith developing cognitive and self-regulation functions [37].

It is therefore suggested that the matrix of oxytocin, cortisol and melatonin levels may represent hormonal hypothalamic influence on the generation of executive functions and goal directed behaviors which in turn are the fundamentals of the emerging cognitive capacities in the newborn [44,46].

3.5.2. Methylation in the oxytocin, cortisol and melatonin systems

The compromised neuroendocrine impacts of premature birth on self-regulation and cognition are apparent in the methylation level beyond the immediate impact of the neuro-hormonal release level. An extensive variance was found in the degree of methylation of the OXTR (at CpG site −924) in 5-month old infants [78]. In these infants, OXTR methylation (OXTRm) levels ranged from 47.91% to 67.98% ($M = 59.57$, $SD = 4.22$). This range/variability is comparable to that reported in two studies of healthy adults (at CpG site −934): 33%–72% methylated ($M = 48.97$, $SD = 7.00$) [115] and 29–61% methylated [68].

When studying infants and their mothers at 5 and 18 months of age, it has been further reported [77] that while the OXTRm levels (assessed from saliva, at CpG site −924) in the mothers remained relatively stable over these two measurement times ($r(90) = 0.960$, $P < 0.001$], this correlation ($r(81) = 0.774$, $P < 0.001$) was significantly weaker in the infants (Fisher's r to $z = -5.87$, $P < 0.001$). After performing additional statistical analyses, the authors concluded that OXTRm is more dynamic in infants than in mothers. In the infants (but not in the mothers), while the group mean methylation level remained stable, an equal number of infants showed an increase or decrease in OXTRm over time. Furthermore, the range of change was nearly double in infants (17.60%) compared to mothers (9.70%) and the variance of infant OXTRm change was significantly greater than that of mothers [77]. It is possible that these developmental changes correspond to infant sensitivity to environmental changes while the up and down fluctuations in methylation levels may start in early infancy and may represent a "maturational" process towards a more "narrowed" range, as the OXTR receptors become available.

Using functional near-infrared spectroscopy while showing faces expressing different emotions at 7 months of age, researchers have further reported that infants with higher OXTRm at 5 months showed increased responses in right inferior frontal cortex to angry and fearful and decreased responses to happy faces, compared to infants with lower OXTRm [78]. The authors found similar results in adults [115], concluding that their results suggest persistence into adulthood. This conclusion may be further developed to hypothesize that the time window for methylation-range consolidation or "maturation", in a manner which persists into adulthood, may be before 5 months.

Furthermore, early life experience can influence OXTRm and its behavioral consequences. Research has shown that less early parental care resulted in higher OXTRm in the blood and brain of infant prairie voles (at CpG sites −934_1, −934_2, −924 and −901, a region of the human *OXTR* that is conserved in prairie voles) [107]. In a translational study, these authors further reported in humans, that maternal engagement at 5 months postpartum significantly predicted (with a weight of beta=−0.3 in the model) a reduction in OXTRm over time (from age 5–18 months). This analysis took into account several potential mediators, including infant gender and infant engagement. The authors conclude that the endogenous oxytocin system, and particularly OXTRm, can be modified by the early caregiving environment mothers [77]. Thus, it may be proposed that positive care giving may reduce the OXTRm and their range, beyond that reported for the first half year of life and that OXTRm levels are sensitive to early adversity vs. positive care giving, pointing to the type of environmental inputs that may affect the hypothesized "maturational" process of OXTR methylations.

In accordance with our last conclusion above, abuse in childhood has been shown to be associated with increased OXTRm (measured in this study at CpG 5,6, or MT, an area in which they measured 20/27 CpG sites) and less gray matter volume in the left orbitofrontal cortex compared to non-abused controls, [53]. In this study, the authors also reported that OXTRm levels were negatively correlated with gray matter volume in the left orbitofrontal cortex. The results suggest that childhood abuse impairs the oxytocin signaling pathway by increasing OXTRm and points to the relevance of NICU stress as a potential adversity highlighting these risks for OXTRm levels.

While the above literature supports the variability and modifiability of OXTRm in infancy, little is known about this before birth or in preterm infants. The one report of increased OXTRm levels at two specific CpG islands in preterm infants' amnion was not supported by corresponding analysis of gene expression [75]. Uvnas-Moberg et al. recently performed a literature search and concluded that they failed to identify studies showing epigenetic changes of the genes for oxytocin or OXTR in relation to physiological birth (and skin-to-skin contact) in humans [133]. The authors suggest that the hypothesized oxytocin related effects may be mediated indirectly through other signaling systems. Additionally, we suggest in light of the studies on term born infants, that "maturation" of OXTRm in preterm infants should be studied around the end of the first half year of life (corrected age) with correction for their GA at birth.

As noted earlier, preterm infants typically have lower levels of cortisol than term born infants at discharge from the hospital [102] and severely sick preterm infants have been shown to display lower cortisol levels than healthy preterm infants [49]. Recently, this has been connected with epigenetic changes in glucocorticoid receptor gene (NR3C1) expression.

Increased infant NR3C1 promoter methylation is associated with prenatal maternal depression [35,104]. Accordingly, infants of mothers that experienced considerable prenatal stress showed increased NR3C1 promoter methylation, increasing the adult-onset health risk [99]. Newborn neurobehavioral outcome (more hypotonia and lethargy) has been reported to be associated with elevated NR3C1 promoter methylation in the placenta [35]. These results suggest that increased methylation of NR3C1 may reach a high point beyond optimal ranges where they program a risk for later life and even through adulthood. This supports our view that healthy development is dependent on optimal ranges of methylations during development.

The postnatal criteria of preterm infants (gestational age, Apgar scores and NICU admission) have been shown to be associated with increase in methylation of NR3C1 (from day 0 to day 4), possibly affecting cortisol regulation [73]. This study further reported less methylation in 3 CpG sites and more methylation in 1 CpG site of the NR3C1 gene in very preterm newborns compared to term controls at birth. In a comprehensive review, the NICU related stress has been related to methylation changes in several genes, including NR3C1, which showed a complex pattern in which in some studies preterm infants displayed greater NR3C1 methylation rates leading to complications and a need for glucocorticoid administration, while other studies showed that preterm infants with greater medical acuity had less methylation [26].

Therefore, it may be the case that the prematurity delays the "maturation" of NR3C1 methylations and that very early born infants experience a given stressor with a greater impact on their physiological systems, and thus remain at risk of developing a problematic "stress reaction" which may be prolonged to later development. These results, as suggested here, indicate a developmental progress potentially starting from fetal life, a topic still to be studied, as well as the crucial impact of GA at birth on this process. The complex pattern of results regarding NR3C1m may point to the unstable levels of methylations in preterm infants during their stay in the NICU which may potentially be related to needed process of methylation "maturation" towards an optimal range is properly supported.

Focusing on DNA methylation in CpG sites 1–4 of promoter region 1F of NR3C1, a study of preterm infants born <1,500g at discharge [54] reported that mean percent methylation at these 4 sites ranged from 0.26 to 0.62. This study further reported lower methylation at CpG site 1 for infants in a high medical risk group (mean birth GA 26.6 weeks, birth

weight 921 g) (M = 0.336, SE = 0.084) than infants in a low-risk group (mean birth GA 30.9 weeks, birth weight 1242 g) (M = 0.617, SE = 0.109, P = 0.032). In accordance with our earlier claim regarding NR3C1, the authors of this latter study suggested that lower DNA methylation of NR3C1 in high-risk infants "may allow for increased binding of transcription factors involved in the stress response, repair and regulation of NR3C1. This may ensure healthy growth in high-risk preterm infants over increasing cortisol levels."(p.68). It is noted that the range of methylations in this latter study is considerably large which may potentially indicate that fluctuation between high and low methylations, that may potentially represent a "maturational" process towards more stable and optimal range of methylations occurs during the NICU experience.

In another study, preterm infants at high risk compared to those at low risk for neurobehavioral problems showed more methylation for NR3C1 and decreased methylations for 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), the gene for the protein that catalyzes the conversion of cortisol to the inactive metabolite cortisone [84]. In this study of 67 preterm infants (GA 23–35 weeks), sampled from cheek swabs a few days before discharge, mean percent methylation levels ranged from 0.2 to 0.55%, showing again a large range, which allows for the possibility of fluctuations in methylations levels during the NICU experience. Therefore, it is possible that a wider range of methylations including up and down frequent fluctuations is part of early stages of a "maturational" process towards greater consolidation after discharge and later in infancy.

In a study of 19 preterm infants (GA 24–28 weeks, NR3C1 methylation rates in promoter 1F region: (1) between birth and postnatal 1 month were stable at all of the 39 CpG sites examined (2) increased significantly between postnatal 1 and 2 months at 9 of the 39 CpG sites examined (3) were affected negatively by antenatal glucocorticoid administration and standard deviation of birthweight (4) [72]. In this study, mean percent methylation levels ranged from ~0.15 to 1.6%. Therefore, glucocorticoids may be supportive for speeding up the "maturational" process towards minimization of the high-to-low range fluctuations of NR3C1 methylations and maintenance of a more optimal stress reactivity in preterm infants. Overall, though data are scarce, it seems that the "optimal range" of methylations is smaller in term born and older infants than the ranges found in preterm infants without external administration. This also may represent the potential supportive role of interventions in the NICU for this suggested "maturational" process of methylations.

As noted earlier, flaccidity and lethargy in the high-risk preterm infants and their associated low levels of crying and protest [7], correspond with high levels of cortisol levels in late pregnancy [38] and thus support the interpretation of the protective role of cortisol before term age. Again this implies that an 'optimal' range appears to be appropriate for adaptive development. In this context it is also relevant that skin-to-skin contact provided to preterm infants in the NICU significantly reduced expression of the NR3C1 gene, as assessed before hospital discharge [66].

Since melatonin has been shown to regulate the production of antioxidant enzymes via epigenetic alterations of the Nuclear factor erythroid-2-related factor 2 (Nrf2) gene [29] melatonin also appears to play a role in countering negative programming effects that are attributed to oxidative stress in compromised pregnancies.

Redox homeostasis is essential for normal health and survival of the cell. Fetuses and newborns are particularly vulnerable to oxidative stress and damage due to their high oxygen consumption, weak antioxidant systems and their inability to induce anti-oxidant defenses during the challenge of birth [82]. Oxidative stress occurs as a consequence of the homeostatic imbalance between oxidant production and intercellular antioxidant systems. In preterm infants, oxidative stress impairs cellular functions and puts them at risk for tissue alterations. Preterm infants are highly vulnerable to oxidative stress injuries due to the high energy demand for survival and growth and the immaturity of the antioxidant systems including secretion of melatonin by the immature pineal gland, among other reasons [82].

The oxidation of DNA causes mutations and damages to the DNA while also altering the chemical structure of nitrogenous bases and forming new bases by these changes in the amino acids chains. The pineal hormone melatonin is one of the molecules that produces antioxidant activity [23]. As oxidative stress can result in genome damage and changes in DNA methylation, including the temporal sequence of epigenome formation [122], it is important to note that exogenic melatonin increased the expression of the NRF-receptor [131,143].

A study of umbilical cord blood in 181 term-born infants reported 3.16 ± 0.52% DNA methylation at the Nrf2 gene promoter [96]. This study further reported that prenatal exposure to arsenic, lead and mercury, potentially toxic metals, significantly increased methylation at the CpG2 site (at low selenium levels), although this was not associated with Nrf2 expression. Thus, methylations on this gene are modifiable, and variation exists. However, we have not found reports on variability in Nrf2 methylation in preterm infants. The investigation of a suspected wider range of Nrf2 methylations and their fluctuations in preterm infants prior to the age of 6 months is warranted. The numeric optimal range of Nrf2 methylation and its (hypothesized) narrowing process over time in preterm infants remains still to be studied.

Based on biochemical reviews in other populations too, the limited data on methylations in preterm and term born infants reviewed above suggest that the compromised hypothalamic process reviewed here starts at a cellular level. Specifically, (1) a common allele of the *OXTR* gene has been related to changes in hypothalamic structure [129]; (2) The variations found in NR3C1 have been related to a complex interplay between extensive splicing and the distribution of N-terminal protein isoforms [81]; and (3) the variability found in Nrf2 methylations has been related to the melatonin molecule's capacities as an oxygen scavenger [36]. Thus, the availability of receptors which correspond to an optimal range of methylations as suggested here, may go beyond the numeric quantity of receptors and relates to the receptors' composition as well, which in turn is governed by production of protein isoforms [81,129]. In summary, the noted variations in methylations, whether induced by genetic factors or by external exposure [10,103] suggest that the adaptability of the growing preterm infant to his\her extra-uterine environmental requirements, through DNA insults vs. transcriptional potential recovery, starts at a cellular level on a match-mismatch trail [34,119]. It is further suggested here that these noted variations are initially dependent on proteomic construction to modulate gene expression (e.g. through alternative splicing) [127] in hypothalamic pathways and its developing circuitry.

The variability documented in the methylations of OXTR, NR3C1 and Nrf2 may point to the hypothalamic regulation work in concert with the epigenetic effects to bring about an optimal range of receptor availability. Compensatory transcription processes may be involved in the hypothalamic pathways thus further pointing to the importance of early interventions in the NICU.

4. The hypothalamus and its cortical connections

To understand the relevance of hypothalamic pathways to self-regulation and cognitive development, we outline here the bi-directional signaling of the hypothalamus and cortical regions in a back and forth developing manner. Furthermore, it is suggested that the compromised contributions of oxytocin cortisol and melatonin in the preterm infant in intensive care, may negatively impact the frontal/prefrontal interconnectivity with subcortical regulating structures such as the hypothalamus as we will detail below. These structures are relevant for the emergence and continuous development of cognitive and self-regulation functioning.

The hypothalamus is an organ of neuronal control that supports homeostasis through its connections with many other brain regions, among them frontal and prefrontal cortex [137]. The hypothalamus

consists of four anatomical parts that include the pre-optic, anterior, tuberal and posterior areas. There are three major regions of nuclei groups and fiber tracts, namely the lateral, medial, and periventricular hypothalamus, each with different structural neural connections to the frontal and prefrontal lobes [137].

Stimulation of the posterior areas of the hypothalamus elicits arousal in cortical activation and motor activity, as well as in sympathetic reaction. Hyper arousal which is associated with compromised cognitive and self-regulation function [5] may result in behavioral stress through connection with endocrine activity coordinated by the hypothalamus and the pituitary gland.

The amygdala–prefrontal cortex–lateral hypothalamic network is associated with cognitive and self-regulation control over behavior [114]. In an animal model, the baso-lateral and central nucleus areas of the amygdala send projections to distinct LH areas (dorsal and ventral, respectively). The mPFC projects to the LH. This can be an additional pathway for mPFC effects on the amygdala [118]. As described above, research shows connections from the prefrontal cortex, considered the seat of executive function, planning, decision making, and behavioral regulation, to the hypothalamus, which act in a bi-directional manner [118]. It is known that the ventral and medial areas of the PFC have extensive projections to the hypothalamus and they further may play a role in cognitive and self-regulation development modulated by the projections to and from the hypothalamus [63].

5. Early interventions, cognitive and self-regulation development, cortical areas and the hypothalamus

A Cochrane review concluded that early intervention programs for preterm infants have a positive influence on cognitive, self-regulation and motor outcomes during infancy, with cognitive and self-regulation benefits persisting into preschool and school age [126]. However, these interventions' locus of impact and underlying mechanisms are rarely studied to date. We suggest here that hypothalamic pathways may be viewed as this hypothesized locus of early interventions impact. The interventions studied, which are widely accepted, have implications for broader clinical implementation. Improved cognitive and self-regulation development have been related to several parameters: Hospitalizing preterm infants in single family rooms versus open bay units resulted in (among other effects) better attention and less physiologic stress [83]; Early interventions)with children born preterm and/or at social risk (focused on the family were associated with increased cognitive and motor development, reductions in parenting stress, maternal anxiety, and depression, increased maternal sensitivity and positive short and long-term effects on infant neurobehavioral outcomes [50,139]; Breast milk, timing and dosing of nutritional intervention contribute to brain and cognitive development in preterm infants [123]; Exposure to music in the NICU improved cardiopulmonary measures [9]; Neuroprotective and neurorestorative interventions, including pharmacological, parenting, educational, and social factors, exposure to adapted auditory and visual stimuli as well as minimization of painful experiences have been shown to enhance cognitive and preterm brain development [135]; Increased parental touch and Kangaroo Care (skin-to-skin contact) have several effects in preterm, low birthweight and term infants, including increased duration of deep sleep and quiet awake states, improved parasympathetic activity, reduced relative mRNA expression (in the delivery room) of the stress-reactivity genes CRH2, *NR3C1* and the serotonin transporter gene (*SLC6A4*), and reduced length of hospital stay [14,22,46,66,101]; and Comprehensive infant behavioral cue based, parent-integrative, individualized developmental care (NIDCAP – Newborn Individualized Developmental Care and Assessment Program) results in improvements in preterm and low birthweight infants in several medical, physiological and neurobehavioral domains as well as in discharge at a younger post-menstrual age [4,76,89,90,97,109,140,141]. Interestingly, imaging studies of interventions in preterm infants showed positive effects on (1) cerebral white and gray matter at the cellular level [135] and (2) improved functioning of the frontal lobe [5]. Therefore, it is suggested that hypothalamic complex regulation through its cortical back and forth projections plays a dominant role in cognitive and self-regulation development of preterm infants and it may be the locus of effects of the early interventions that result in cognitive and self-regulation improvements in this compromised population. We note, that although we emphasized the critical role of hypothalamic pathways for the optimal growth of preterm infants, especially while they are hospitalized in the NICU early in their life, and we suggest the hypothalamus as the locus of impact of early interventions, we acknowledge the additional developing circuitry beyond the immediate hypothalamic internal neuroendocrine and epigenetic signaling activity. In this respect, the hypothalamus may be affected by the impact of early interventions on other regions via their feedback projections, still to be studied.

In sum, the intervention methods aimed at stress reduction in the infant's environmental inputs and at facilitating the internal stressful cues and reactions of the infants show an improvement in cognitive capacities. This suggests that these methods affect the developing HPA axis and the infant's general stress reaction, which in turn may affect the HPG and HPT axes through the crosstalk between the axes, yet to be studied, and may result in better-regulated functionality of the hypothalamus. Arising from this review is the idea that this crosstalk is apparent on epigenetic and biochemical levels as well. Thus, this crosstalk suggests that hypothalamic control may serve as a mediator for improvement in the emerging mental capacities of the infant. This view serves as the basis, the preliminary support and current validation of the model outlined below.

6. A model of early programming of hypothalamic regulation

The complex considerations articulated above lead to the hypothesis of an integrative dynamic model adapted from Control Theory (see Fig. 1). Control Theory originated in Engineering, a subfield of Mathematics, was first described in the 19th century by James Clerk Maxwell and has been developed further to date. Control Theory implies a dynamic regulation of signals by controllers in order to reach a required level of signal compared to a given level of signal. The controller provides the corrected signal following comparison. Essential to Control Theory are the feedback mechanisms and the comparisons between the required and the given signal, behavior, outcome or output [16]. Powers [110] suggested that perceptual cognitions are generated by brain functioning similar to control systems. Perceptual control theory has recently gained renewed interest [25,88]. Accordingly, our model postulated here represents a dialogue between the preterm infant and his\her environment as it develops towards the infant's seminal perceptual capacities, which are the seeds of cognitive development later in life. The crucial role of the infant's actual neurobehavioral reactions as well the nature of the infant's environment and his/her genetic predisposition are represented. The environment includes the stressful conditions and the supportive alterations and interventions for stress reduction. The match-mismatch between the infant's capacities and the given environment determine the infant's efforts toward homeostasis in a continuous process that engages the hypothalamus with the neuroendocrine and neuropeptide factors it controls, as well as the epigenetic changes in receptors in prefrontal cortex. According to this model, comparisons of the behavioral output to inputs from the hypothalamus and the epigenetic level ultimately are processed within the prefrontal cortices. The model shows the bi-directional projections between the hypothalamus and the prefrontal cortex with feedback evaluation of the gap between environmental requirements and genetics as inputs and the preterm infant's responses and reactions as an output. This is understood as an adaptive process which contributes to the reduction of the gap following a correction signal sent from the hypothalamus and the epigenetic level to the prefrontal cortex for final evaluation and decision making regarding the neurobehavioral output.

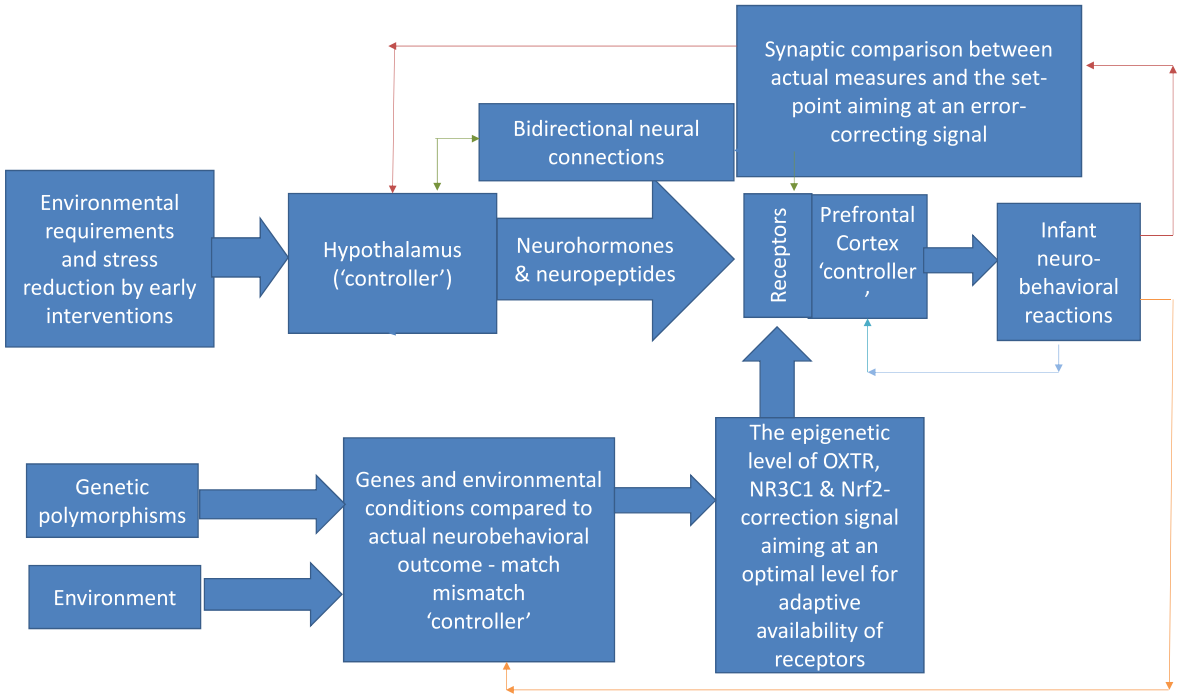

Fig. 1. This model describes a multivariate control system diagram. The figure is designed in accordance with control system diagram requirements [40]. It describes the hypothalamus as a 'controller' of homeostasis and the epigenetic expression as a second 'controller' of receptors availability. A third 'controller' is described to address the prefrontal action. Three 'feedback mechanisms' are shown for each of the three 'control systems' with the different inputs compared to the same output (infant neurobehavioral reactions). Each of the first two 'controllers' comparisons result in 'correction signals' transmitted to the prefrontal cortex, which in infancy is relatively immature, emphasizing the role of lower brain regions such as the hypothalamus. Thus, the prefrontal cortex is not considered a 'master controller' as would be the case for the adult healthy brain. However, in our model it is suggested that the final evaluation for executing neurobehavioral action is carried out by the prefrontal cortex. According to early evolutionary postulates by J. Hughlings Jackson [69] we assume that the controlling role of the prefrontal cortex fluctuates through development. Therefore, the best way to describe it is by the fed forward and fed back mechanism shown for the bidirectional neural connections between the hypothalamus and prefrontal cortex. The neurohormonal level feedback loop is described by red lines, the bi-directional connectivity loop is marked by green lines, the epigenetic feedback loop is marked by orange lines and the feedback loop to the PFC is marked in light blue lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The interventions for stress reduction are included as an additional input. The model describes the manner in which the interventions may be beneficial for improved cognitive and self-regulation functioning, based on feedback from one output, namely the emerging neurobehavioral reactions of the infant. (See Fig. 1).

In the model (see Fig. 1), the hypothalamus is one of three 'controllers'. It receives signals from the environment about the environmental requirements. As a result of these inputs, the hypothalamus regulates levels of neuro-hormones and neuropeptides. The resulting signals are analyzed and projected to the prefrontal cortex. The hypothalamus and the prefrontal cortex share bidirectional neural connections. The infant's resulting neurobehavioral reactions, the basis for the development of infant cognition, are compared with the environmental requirements including the support provided by the interventions. The comparison results are fed back to the hypothalamus for correction of its signaling. In turn, the neuro-hormone and neuropeptide production levels are adjusted accordingly. A separate controller is suggested for the gene methylations for the neuro-hormone and neuropeptide receptors and their prefrontal receptors' availability. This 'controller' receives genetic polymorphisms and environmental conditions as inputs and generates epigenetic changes such as alterations in DNA methylations as output and aims at a developmentally supportive, optimal range on a match-mismatch basis [119,136]. The gaps between those measurements and the actual reactions of the infant are crucial for the comparison. The comparison results are fed to the controller of methylation, which, in turn, affects the receptors' availability and production in the prefrontal cortex and other postsynaptic areas.

The prefrontal cortex is presented as a third 'controller', which aims at sending the final command for the behavioral output through a process of evaluations of its inputs from the other two 'controllers' and the feedback from the recent output of neurobehavioral reactions. According to Jacksonian postulates [69], higher and phylogenetically newer circuits inhibit lower and phylogenetically older circuits. However, according to Jackson, when a higher circuit is compromised, older circuits are dominant. In infancy, the prefrontal cortex is still developing, and in preterm infants this region and its circuits are immature. Thus, according to the Jacksonian validated view, the role of the hypothalamus increases in this condition. Therefore, in this model the prefrontal cortex is considered a third 'controller' rather than a 'master controller'. The three controllers share the same output of neurobehavioral infant responses and reactions. The coordinated function of the three controllers appears on the cellular level of the receptor's activity including its composition and numeric availability in prefrontal cortex, and thus likely affects cognitive and self-regulation development. Further coordination between the three controllers appears in the bi-directional neural projections between the hypothalamus and the prefrontal cortex while the hypothalamus aims to secrete and regulate signals, which will maintain homeostasis and an optimal level of receptor functioning in accordance with environmental stress alterations. A 'control system' that comprises three 'controllers' with feedback mechanisms is suggested for the chemical and epigenetic activity with a bidirectional connection between the hypothalamus and the prefrontal cortex. A 'controlling signal' from the hypothalamus is transmitted to the prefrontal cortex, and a signal from the prefrontal cortex is in turn transmitted back to the hypothalamus. This mechanism implies that signals are initiated either by the hypothalamus or the prefrontal cortex and are transmitted to the prefrontal cortex and/or the hypothalamus, respectively.

We suggest a model that uses a control action by the hypothalamus (one controller), its associated methylations (a separate controller) and the final evaluation within the prefrontal cortex (another separate controller) in a progressive fashion in the infant's brain in order to support the brain's return to balance without undue delay or haste which might challenge the stability of prefrontal development under conditions of stress and its reduction by early interventions. Therefore, it is suggested that for the interventions, especially the comprehensive NIDCAP intervention, which showed improvement in cognitive and regulatory development, corrective and adjusting parameters are implemented. They affect the hypothalamus, its epigenetic basis, and in turn, the prefrontal receptors' availability. The model suggests that the hypothalamus, its epigenetic levels, and the coordinated final decision making and projections from the prefrontal cortex function as mutual regulators and monitor the controlled process of stress reduction, while continuously comparing it to the set point, the environmental conditions and stimuli. The difference between the infant's actual and adaptive (expected\required) reactions and responses serves as the error signal that provides feedback in order to generate a control action in the hypothalamus, its epigenetic level and the prefrontal cortices, and brings the infant's reactivity, comprised of multivariate components, to the optimal activity and reactivity level for frontal functioning in a given condition or situation. As the NICU is a stressful environment and it has been shown that it affects brain development of preterm infants beyond the effects of prematurity [30], we further suggest that the interventions that were found to be effective work though hypothalamic pathways, which are involved in the developing stress reactivity and its bi-directional pathways with the prefrontal cortex.

In this model we propose that the smoother the error correction signaling process is, the smoother the adaptation to new age-appropriate goals will be. This may represent the "hypothalamic resistance response" to the stress encompassed in the transition. By mentioning the term "hypothalamic resistance response" we aim to summarize the conceptualization of a well-working hypothalamic control system during stressful conditions and inevitable transitions implying that when the hypothalamus is less "resistant", its multi-level control system may suffer from dysregulation of the error correcting process by signaling the error to the "controller" without being able to adapt a proper correction as a new required set-point has yet to be established for the control system to work adaptively during a transition.

This model may also be used also as a diagnostic tool to locate "alarms" within the measures of the "controllers" by comparing a simple blood test matrix result of the hypothalamic neurohormones mentioned here (and a more complex analysis of methylations on the genes for their receptors), to the level of behavioral adaptation during very early development. This model also paves the way towards the development of pharmaceuticals based on pharmacogenomics to target the availability of receptors beyond supplying replacement of the neurochemicals or pharmaceuticals that manage reuptake. This may also be applicable to distinguish between adaptive and maladaptive conditions. Maladaptive conditions may occur when the required value, the set-point of each "controller", in the suggested control system needs to be shifted as a result of the need to experience a transition. This is especially important as the basic level of the suggested control system in the model, the level of epigenetic reactivity, has been shown to be sensitive to environmental inputs which potentially suggests effects on the transcriptome.

6.1. For further research

The hypotheses derived from this model require the integration of the three axes and their endocrine secretions and neurostructural components as well as the associated methylation levels and variations to be included when investigating a condition, a transition, or an intervention in early development as the independent variable. The three levels suggested here, the epigenetic, neural\structural and the hormonal, should be integrated into one study optimally. In early born infants a structured observation of neurobehavioral reactions [46], while the infants are undergoing a supporting caregiving process, may be investigated concomitantly with EEG measures for unraveling the coupling between the infant's behaviors with the EEG signals, including any correction of Tracé Alternant, which is a typical EEG picture after birth. Such a study may show, in a repeated measures design, whether behavioral stressful vs. regulated behaviors are coupled with different and identifiable EEG waves at the same time of measurement and in a corrected manner over time if supported by early intervention.

The hypothesized "maturational" process that methylation levels undergo in preterm infants and critical time windows for this process requires further longitudinal research. A crucial investigation would be to determine numerically an optimal range of methylations as associated with adaptive\maladaptive neurobehavioral reactions and compare them between term and preterm born infants. The investigation of pharmacological and non-pharmacological interventions impacts on the suggested "maturational" process of methylation levels for potentially narrowing their large range to a more adaptive narrower and optimal range remains for further studies.

Another scientific question of significant value which arises here is whether the hypothesized maturational process could be speeded up in preterm infants to facilitate the early programing of their stress reactivity and its impact on later development. Finally, research aimed at the use of methylation levels as a predictive\diagnostic tool is warranted.

7. Conclusions

In summary, this paper aims to present an integrative review and view, which shows the centrality of the hypothalamus in generating adaptive neuro-hormonal and neurochemical reactions, which affect the brain regions responsible for higher level cognitive, self-regulation and executive functioning. It is concluded that the interventions that show improved cognitive and regulation scores in the treated preterm infants compared to the controls, exert their effects via the hypothalamus through reduction of stress due to the NICU environment and subsequent release from hospitalization. Furthermore, it is concluded that optimal homeostatic control by the hypothalamus including its interactions with projections to the frontal lobes, is responsible for cognitive regulatory development. This control is a second-by-second process of the infant's response and reactivity to a given condition or situation via the immature hypothalamus. Moreover, it is suggested that infants evaluate the environmental conditions continuously and relate to them through hypothalamic regulation. Furthermore, we suggest that early intervention may work as an error correction factor on the transcriptional level. We also emphasize the role of stress reduction in the developing crosstalk between hypothalamic axes. We term these overall hypotheses as a "hypothalamic resistance response". This, in turn, especially in conditions of stress reduction, has profound effects for the improvement of preterm-born infants' cognitive-regulatory status in infancy and later childhood. The control systems model delineated here integrates the multi-level impacts of hypothalamic pathways on neurobehavioral developmental reactions in preterm infants by outlining their second-by-second endogenous and exogenous driven error-correction processes.

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Contributors' statement

Sari Goldstein Ferber, PhD and Aron Weller, PhD conceptualized and planned this review in collaboration with the other co-authors. They wrote the first draft. The other co-authors reviewed, commented and edited the manuscript.

Heidelise Als, PhD refined conceptualizations, critically reviewed drafts, assisted in analysis of data, commented, and added significant contributions to the text.

Gloria McAnulty, PhD provided relevant literature, interpreted findings and critically reviewed the various drafts of the paper. Gil Klinger, MD, contributed refinement of medical data, critically reviewed drafts, assisted in analysis of data, commented, and added significant contributions to the text.

All authors reviewed and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Declarations of competing interest

None.

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