Development of the ontogenetic self-regulation clock

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Abstract

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To date there is no overarching proposition for the ontogenetic-neurobiological basis of self-regulation. We suggest that the balanced self-regulatory reaction of the fetus, newborn and infant is based on a complex mechanism starting from early brainstem development and continuing to progressive control of the cortex over the brainstem. We suggest that this balance occurs through the synchronous reactivity between the sympathetic and parasympathetic systems which both develop from the brainstem. We present an evidence-based approach in which by inhibition-excitation balance, neurotransmitters, cardiovascular and white matter development are dependent on this synchrony, including the postnatal development of EEG waves and vagal tone and show developmental milestones in term and preterm infants. We term this ontogenetic stepwise process “the self-regulation clock” and suggest that this clock is located in the largest connection between the brainstem and the cortex, the corticospinal tract. This novel approach paves the way towards more accurate hypotheses and complex studies as well as pointing to time windows for interventions in preterm infants. We suggest an ontogenetic biologically-based theorem for the developing capacity of self-regulation in early life including milestones for a time pathway from fetal life to infancy. We suggest novel hypotheses for molecular, structural and functional investigation of the “clock” circuitry suggested as responsible for the developing self-regulation and its neurobehavioral correlates

Contribution to the field

This is an overarching paper, which suggests a novel neurobiological basis and integration of scientific knowledge, and provides a breakthrough in understanding of embryonic and early life beyond the behavioral and theoretical previous conceptualization of self-regulatory functions. The paper suggests a a novel theorem and derived testable hypotheses on the developmental biological trajectory of self-regulatory functions including a neural circuitry not suggested earlier.

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Development of the ontogenetic self-regulation clock

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Abstract

To date there is no overarching proposition for the ontogenetic-neurobiological basis of self-regulation. We suggest that the balanced self-regulatory reaction of the fetus, newborn and infant is based on a complex mechanism starting from early brainstem development and continuing to progressive control of the cortex over the brainstem. We suggest that this balance occurs through the synchronous reactivity between the sympathetic and parasympathetic systems which both develop from the brainstem. We present an evidence-based approach in which by inhibition-excitation balance, neurotransmitters, cardiovascular and white matter development are dependent on this synchrony, including the postnatal development of EEG waves and vagal tone and show developmental milestones in term and preterm infants. We term this ontogenetic stepwise process "the self-regulation clock" and suggest that this clock is located in the largest connection between the brainstem and the cortex, the corticospinal tract. This novel approach paves the way towards more accurate hypotheses and complex studies as well as pointing to time windows for interventions in preterm infants. We suggest an ontogenetic biologically-based theorem for the developing capacity of self-regulation in early life including milestones for a time pathway from fetal life to infancy. We suggest novel hypotheses for molecular, structural and functional investigation of the "clock" circuitry suggested as responsible for the developing self-regulation and its neurobehavioral correlates

Introduction

There are accumulating data on the stepwise process of autonomic nervous system (ANS) maturation and its coupling with cortical development, e.g., (1). In addition, the literature highlights different trajectories for the gradual development of the ANS in fetuses and preterm infants, emphasizing the essential role of both branches of the ANS as well as the role of the progressive development of the brainstem in the development of these two branches from early stages of gestation onwards.

The roles of the sympathetic system and the arousal states required for executive functions have been considered (2–7). The role of the parasympathetic system in the development of these functions has also gained much attention (8,9). However, the interplay between the two subsystems of the ANS, components that affect or delay the establishment of the synchrony between the two systems, as well as the developmental gate for this synchronous occurrence have been neglected, although implicated, in general, in the theoretical concept of self-regulation. As both the sympathetic and parasympathetic systems originate in the brainstem, the brainstem has a crucial role in the emergence of synchronized control of self-regulation. In this paper, we focus on the brainstem's developmental impact on both the ANS and the developing cortex as related to the emergence of self-regulation, a prerequisite for later appearance of executive functions. We suggest that ANS maturation occurs within the developing control of the cortex over the brainstem through particular neurotransmitter interchange originating in the brainstem. We also present a neuro-anatomical perspective for cortical-brainstem connectivity through the corticospinal tract (CST). We further suggest that cortical coupling with the ANS is essential for brain inhibition-excitation balance within the developing organism and that this synchrony is a required condition for accomplishing the interplay between the sympathetic and parasympathetic systems. This is in accordance with recent views showing that greater phasic ANS reactivity starting from relatively low tonic (pre-stimulus) ANS activity is associated with improved executive functions during infancy and childhood (10). We suggest that ANS synchrony is achieved following cell migration from the brainstem to the cortex and the crucial interchange of neurotransmitters affecting proliferation, differentiation and the onset of myelination processes, and occurring at the time window of mid-gestation through the first two years of life. This time window has been identified as a period of excitation-inhibition development which results in a mature balance and parallels the neurobehavioral conceptualization of self-regulation. We also suggest that the development of this ANS synchrony is programmed early in life and that it depends on brainstem maturity. It is moreover suggested that this process follows an ontogenetic clock in term born infants while in preterm infants the phase shifts in their clock put them at neurodevelopmental and cognitive risk. Based on the theoretical concept of intra-individual self-

regulation, which has been studied earlier (11–13), we suggest the term "self-regulation clock" to describe the developmental milestones of ANS synchrony from gestation to the first two years of postnatal life. This "clock" is presented as the early prenatal and postnatal source of executive functioning emergence through gradual, more differentiated and sophisticated, eventually goal directed, responses to the environment and care. We base our postulates on neuroanatomical, neurochemical, EEG and MRI data as well as on vagal tone measures, cardiovascular development and connectivity with the maturing cortex.

Self-regulation: An intra-individual perspective

There are two approaches to early life self-regulation: an intra-individual (infant) and inter-individual (infant self-regulation in the context of interactions with the caregivers), both of which address the regulatory difficulties of term and preterm infants, but from different angles (13–18). The intra-individual approach's relevance starts from gestation and the generation of the ANS in the fetus, while the inter-individual approach focuses on the measures of the child's mutual interaction with his\her parental environment postnatally (Raffaelli *et al.*, 2005; Kopp, 2009; Swingler *et al.*, 2015; Taylor and Clark, 2016). In the current review, we focus on the intra-individual approach both prenatally and postnatally while the environment (including the parental environment) is regarded as an input (whether balancing, mobilizing or interfering) to the growing individual.

The intra-individual approach, while viewing the parents/caregivers as the primary co-regulators of the child across development, assesses the strengths and thresholds of the infant during moments of reactivity to environmental requirements. The unique view of this approach lies in the focus on the infant rather than on the dyad, viewing him/her as a capsule that manages internal and external cues. This approach views the infant as a coping individual on his/her own although needing facilitation and support (3). It is applicable to the growing fetus in the womb with placental influences and to preterm infants exposed early on to the extra-uterine environment, which is less accommodating than the uterus. Regulation according to this approach has been defined (23,24) as the ability of the organism to return to baseline after mounting specific responses to an environmental stimulus. Intrapersonal neurobehavioral co-regulation is defined as the capacity of the organism to subordinate all neurobehavioral capacities to enhance learning that allows it to be adaptive to the environmental requirements. It is also defined as the capacity of the organism to return to balance, following adaptation of the enhanced neurobehavioral subsystem to the environmental stimuli (24,25). These processes support the successive maturation of all neurobehavioral subsystems, i.e.,

autonomic, motor, state and attentional (2,3), while working together and in competition with each other, towards a coordinated increasingly differentiated balance by increasing or decreasing responses to each other's state starting from early gestational age (GA) (Figure 1).

Self-regulation encompasses all neurobehavioral outcomes in the fetus, newborn and infant, which result from ANS synchrony (16,18,26). These are shown in the motor, state and attention subsystems (2). These subsystems work in concert in normal development by subsystem-specific contribution to the other subsystems, in every new developmental acquisition, in accurate time windows, with an inhibition-excitation manner, and serve as the basis for the maturing executive functions. Maturation of the self-regulation clock is delayed by prematurity. This is evident in extreme sympathetic or parasympathetic imbalance and lack of ANS synchrony. These extreme conditions are also dependent on state subsystem organization and its prematurity and are affected by internal and external cues (18).

The importance of the parasympathetic system in regulating over-arousal as well as that of the sympathetic system in bringing the infant up to the arousal level needed for executive functions has been noted earlier (8,13,16,27). However, the focus on the synchrony between the two systems as one working system aimed towards an ongoing balanced activation has not been elaborated in the scientific literature. Our postulation follows a well-established concept of a required continuous balance between excitatory and inhibitory brain functions suggesting that any deviation may put the individual infant at risk for adverse development (28). This balanced activation, widely mentioned in the literature on the concept of self-regulation (e.g., (29–31), is supposed to rescue the newborn from over-arousal and exhaustion as well as from systemic shutdown states. We suggest that when achieved, this synchrony is the first step in the replacement of brainstem control by the developing cortex, thus supporting the trajectories of emerging cognition. It is emphasized here that this synchrony is a prerequisite for cortical maturation and the emergence of cognition in the infant, especially in the preterm born infant. To support this view, an author of this review, and colleagues, found that autonomic system measurements predicted Bayley mental scores in the first year of life, in term and preterm born infants (32).

The importance of the neurobehavioral function of regulation has been identified in several MRI and EEG studies of preterm infants (e.g., (27,33)). Additionally, our studies show the interplay between the motor and the state/sleep/awake subsystems in full-term and in preterm infants (i.e., that motor system activation is the source of inhibition of the attention system and vice versa) (25,34). Differential excitation and inhibition are postulated to underlie major developmental breakthroughs and developmental task

acquisitions by the developing infant (2,23,35). Inhibition is necessary for neurobehavioral subsystems supporting a step-response timely acquisition (see below) of a new developmental task (2,26,36,37). Excitation is needed to attract and support the developing infant (as well as the fetus and the preterm infant) in his/her desire to acquire a new developmental task. Thus, the balance between excitation and inhibition is the basis for development of the regulation of all the sub-systems. This balance follows an ontogenetic clock in healthy newborns. It is delayed, while exhibiting a similar gradual achievement of clock milestones, in preterm infants. This maturational process in both term and preterm infants is suggested to be termed as the "self-regulation clock".

Self-regulated acquisition of a new developmental task may be described with the term "step-response", adapted from Control Theory in engineering (commonly used in the field of Neural Networks). The step response of a system in a given initial state consists of the time evolution of its outputs when its inputs are the step functions. In control theory, step response is the time behavior of the output of a general system when its input changes from zero to one in a very short time (38). Accordingly, adapting the approach from neural network theories, timely step-response acquisition of a new developmental task by the child, within the excitation-inhibition axis, follows a self-regulated neurobehavioral path (24). The optimal amount of inhibition and excitation differs by developmental stage. Thus, the balance between excitation and inhibition is the crucial factor in development. We suggest that this balance is the essence of the developing ANS synchrony and its coupling with the cortex, which is the basis for the self-regulation clock (Figure 2).

Self-regulation has been found to be controlled by the brainstem in preterm infants (39,40). Thus, our review of the development of ANS synchrony in the brainstem-cortical circuits, its milestones during gestation and relevance to the emergence of executive functions, including mounting neurobehavioral reactions and return to balance as well as conditions such as over arousal and shutdown, is timely. The developing control of the cortex over the brainstem represents the development of self-regulation as outlined in this review.

Self-regulation, executive functions and the brainstem

We suggest according to (2,35,41) that in the fetus and the newborn, the neurobehavioral subsystems pursue balance through the developing synchrony within the ANS and that accomplished balance is a

source for the emerging of executive function (42)b. Executive functions are defined as control mechanisms that are action-directed (43). They develop from nuclei of neurobehavioral subsystems' interplay, which are achieved at balanced phases of the ANS. This develops further during infancy into diverse developmental accomplishments.

An executive attention network, termed "the cingulo-opercular network" (44,45) (comprised of the anterior cingulate and anterior insula (operculum)), provides the infant with opportunity for voluntary control behaviors in accordance with goals (46). This network is involved in error detection and resolving conflict between signals (45,47,48). The executive network is present in infancy and activates the same regions as in adults (49). (46).

It is accepted that early self-regulation predicts later development of executive functions (e.g. (50)). Early goal directed functions are the germinal capacities for later attention regulation. It has been noted earlier that self-regulation includes inhibition of attention to irrelevant input (51) and effortless control (46) together with emotional arousal to sustained goal-directed behaviors (52) which support, together, early emergence of executive functions to be developed into more differentiated and more sophisticated goal directed behaviors through acquisition of excitation-inhibition balance. This goes hand in hand with our claim on the needed synchronization between the inhibiting functions of the parasympathetic system and the arousal modulation by the sympathetic system at the same time. We suggest that as both systems develop from the brainstem, early corner stones of self-regulation development are based on brainstem development to be further developed by the progressing control of the cortex over the brainstem. This view allows to consider that cognitive flexibility develops from early capacities of self-regulation progressing from the brainstem up to the cortex and places self-regulation as the earliest foundation of executive function and cognitive flexibility development later in childhood.

The development of the self-regulation clock precedes the development of goal directed and executive functions. These successive functions appear in a rostral to caudal pathway emerging from the brainstem through the developing control of the cortex. The goal of this review is to outline this rostral to caudal axis of developing control of the cortex over the brainstem and to show its spatiotemporal development starting from mid-gestation through the end of the second year of life.

Emerging seeds of executive capacities are observed in infants in the orienting reactions to their environment. At infancy individual differences in attention are seen in habituation, novelty preferences,

and focused attention (53). This process is compromised in preterm infants as shown in selective deficits in inhibition, working memory and cognitive flexibility. These deficits are evident at early childhood and persist into adulthood showing a negative association with increasing GA and weight at birth (54–65).

Decreased white matter within the neural connections of the brainstem and the cortex has been observed in adults born prematurely (66,67), supporting the postulates of this review. We and others previously suggested that these alterations may be evidenced by early brainstem neural conductance changes (39,68). Adverse effects of preterm birth on attention and academic outcomes are partially mediated by toddlers' inhibitory control abilities, a function of the parasympathetic system (69). In contrast, a study that investigated a sample of 1,292 children up to the age of 24 months found that high levels of executive function capacities were significantly correlated with high levels of emotional reactivity (or arousal) and high levels of the regulation of this reactivity. Additionally, high levels of reactivity and low levels of regulation were significantly correlated with low levels of executive function (70). These results point to the crucial role of self-regulation, a concept which parallels the neurological concept of excitation-inhibition balance, for the manifestation of executive functions.

In children showing low levels of emotional reactivity, self-regulation was not correlated to executive functions, showing the need for arousal-inhibition balance for optimal executive functioning (70). The results of this latter study suggest the need for arousal and sympathetic system activity for social encounter and executive functions in children in contrast to previous theories that emphasized the major importance of the parasympathetic system for the developing of adaptive social and cognitive control (8).

ANS coupling with the cortex: evidence from the compromised development of preterm infants

Synchrony of the ANS is required for the brainstem's developmental impact on the cortex beyond the effects of the parasympathetic system on the cardiac pacemaker as the sympathetic nervous system affects cardiac contractility (71). Another primary impact of the brainstem on the developing cortex is through ensuring blood flow to the waiting subplate regions which later becomes less transient following the penetration of the thalamic fibers and the establishment of brainstem-thalamic connectivity at mid-gestation (72,73). The earliest afferents that reach the cortical subplate are monoaminergic fibers originating in the brainstem (around 14 weeks GA) (74,75). Thus, the impact of the brainstem on the developing cortex is through direct and indirect pathways within a rostral to caudal spatial progression

along an early-programmed temporal route. These impacts of the brainstem, which facilitates the development of the two ANS branches, on cortical development represent the foundation of the ANS coupling with the cortex in normal development. Recent reports note that EEG 10Hz frequencies reflect the organization of the brainstem network that specifically governs sympathetic outflow (76). Thus, we propose that ANS synchronicity consolidation through the brainstem is a developmental prerequisite for the continuation of cortex development and the emergence of executive functions. We define this synchrony within the ANS physiologically as the balance and crosstalk between tonic and phasic functioning of both the sympathetic and parasympathetic systems regulated by the developing brainstem (77,78).

The sympathetic system, essential for survival, is functioning at first in the presence of an unmyelinated vagus nerve (8). Thus, it develops earlier in gestation than the parasympathetic system and it is affected mainly by the noradrenergic system's development (79). During early gestation, the fetus is protected by the uterine environment and the placenta while the sympathetic system develops. Preterm infants exposed to the extra-uterine environment with an underdeveloped parasympathetic system, suffer from the lack in synchrony between the ANS systems, thus easily and rapidly reaching states of over-arousal and systemic shutdown as shown in their common respiratory and pulmonary diseases such as tachycardia, bradycardia and apnea. The dominance of the brainstem is prominent in preterm infants as they lack ANS synchrony, while in term newborns the relatively developed vagus nerve supports migration of cells to the cortex, thus gating the future emergence of cognition and executive functions.

The synchrony between the sympathetic and parasympathetic systems continues through the first two years of life and shows marked impact on the cortex. The relevance of the sympathetic system for social and executive functions of the infant has been noted (Als et al 1982). Earlier considerations suggested that the vagus and the maturation of the parasympathetic system in general are responsible for the initiation of social and interactive capacities of the infant (8). However, when the need for arousal was mentioned, the need to modulate arousal was emphasized and not the need for arousal per se as an essential mechanism for survival and the emergence of executive functions (80). In addition, shutdown conditions in preterm infants were not explained nor elaborated in past models (11). We suggest that shutdown conditions may arise by the lack of the required arousal. We suggest that sympathetic activity is essential for such capacities and that parasympathetic modulation of arousal turns the ANS into a synchronized mode in the full-term infant. In accordance, in flaccid cases, such as exhibited by preterm infants, sympathetic reinforcement of the too low reactivity may allow synchrony to be restored (25).

Thus, this synchrony of the ANS is required early in development for executive functions to emerge on the pre-programmed route, works in two directions: the sympathetic modulation of the parasympathetic system and parasympathetic modulation of sympathetic activation. Therefore, the emergence of executive functions depends on ANS synchrony beyond myelination of the vagus. We suggest, in contrast to other views (8,81), that deviations from ANS synchrony may occur even in conditions of a mature and myelinated vagus depending on the environmental, including parental, internal inputs and allostatic load (82) setting-up the quality and rate of responsivity of executive functions (83). Thus, it is suggested that shutdown and over-arousal may occur in the growing infant as a result of environmental over-stimulation or too low input load which often occur in NICUs due to misfit between the preterm infant's neural status of development and environmental demands (27,32,84).

The function of the synchronized ANS depends on balanced environmental stimuli and balanced reactivity of the infant. It is a two-way process after birth and it concerns the matching between the infant's internal ANS synchrony in reaction to a given stimulus, thus suggesting that ANS synchrony describes a dialogue between the ANS synchrony of the infant and the available environmental stimuli. The degree of matching conditions between ANS synchrony and the given environmental input defines the optimal range of infant reactions. This consolidates the concept of self-regulation from the intra-individual perspective, while considering the role of environmental input as both enriching and constraining the infant's capacities (Figure 3).

MRI studies show that brainstem-cortex connectivity is impaired in preterm infants (85), which in turn highlights the brainstem's role in the development of cognitive capacities and indicates the time window for the maturation of ANS synchrony and its effects on cortex development (86). For a recent review see also (87).

We suggest that brainstem function is of utmost importance in cases of immature or decreased cortical function exemplified in the conditions exhibited by preterm infants. In cases such as systemic shutdown leading to brain compromise, brainstem function is the most resilient as it is the earliest to develop and the last to shut down. When there is interference in the synchrony of the ANS, higher functions such as executive functions and attention regulation may need to rely on neural connectivity and catabolic synapses in the early developed brain regions with surviving synapses equipped for longer periods of systemic collapse and immaturity. This may explain our results showing a major deficit in attention regulation in preterm infants with an injured brainstem (40). Thus, when both cortical function and

germinal regions such as the brainstem were dysfunctional at pivotal time-windows, the result is an exceptional reduction in executive functions later on in development. Accordingly, recent findings show that preterm birth may alter global, regional and local development of the brainstem even in the absence of white matter injury evidenced in MRI during the postnatal life of the preterm infant (88).

In preterm newborns, the ANS is also immature and may be inadequately prepared for the demands of cardiorespiratory transition at birth (89). Additionally, DiPietro et al. (90) found that fetuses exhibiting slower and more variable heart rates had at age of 2 years significantly higher Mental and Psychomotor Development Indices (MDI, PDI, respectively) on the Bayley scales and they had better speech development than those with faster fetal heart rate implying lower HRV. Similar results show that HRV and MDI scores were associated at the age of 1 year and with standardized cognitive test scores in middle childhood (91). Accordingly, afferent information processing by the intrinsic cardiac nervous system can modulate frontocortical activity and impact higher-level functions (92). These studies connect the cognitive development of the preterm infant to the cardiovascular modulation of frontal activity through ANS functioning, either synchronous or not.

Better cognitive development, associated with increased white matter in the frontal lobe have been found in preterm infants treated with adjusted environmental stimulation known as the NIDCAP method (27) showing the relevance of the environmental input after birth for the developing brain synchronicity. This corresponds to the ontogenetic process of intra-individual and then after birth the additional inter-individual self-regulation. Interestingly, Als et al. (2004) study findings showed increased coherence (reflecting the correlation between spectral content at two electrode points over time on a frequency-by-frequency basis (93)) between frontal cortex and a broad spectrum of mainly occipital brain regions, and higher relative anisotropy in the left internal capsule, with a trend for right internal capsule and frontal white matter. This suggests that cortical synchronicity may be treated in preterm infants within the time window of self-regulation emergence and establishment of major consolidation in excitation-inhibition balance, at mid-gestation ages. This synchrony, mentioned as spectral coherence, representing the corticortical connectivity, can be viewed also as resulting from a relatively synchronous ANS as showed in the results of neurobehavioral assessments which include ANS status (12,16,26,94), in addition to the EEG and MRI results in the Als and colleagues study (27). Thus, it may be suggested that the ANS status protected the treated infants and this resulted in spectral coherence which in turn was found to be associated with higher regions volume development, as found by (27). This view is also supported by a recent study showing that regional density development follows other developmental processes, i.e., cortical development between 25 and 38 weeks GA shows a predominant increase in dendritic

arborization and neurite growth, while between 38 and 47 weeks GA it is dominated by increasing cellular and organelle density (95). We suggest that synchronization through neural arborization represents the development of the balance between excitatory and inhibitory inputs, which precedes cellular coupling.

The crucial milestones of ANS synchrony development and the multi-level consolidation of the self-regulation clock

The progress of the developing synchrony between the sympathetic and parasympathetic systems involves interchanges in the excitatory vs inhibitory role and the maturation of white matter structures. This process is detectable from early gestation through the age of two years of life. We will show the milestones of this process which consists of a crucial time window at mid-gestation, from neurotransmitter, neuroanatomical (as shown in MRI studies) and cortex connectivity (as shown in EEG studies) angles. We will show that reformations along all three angles occur at the same timing during gestation and early development, thus suggesting an essential ontogenetic clock of this development that has specific time windows for a stepwise development and specific trajectories along the same time points.

There are several pivotal processes affecting brain development such as proliferation, differentiation, myelination and cell migration. We will consider the main neurotransmitters involved in this progress. We will emphasize the shift between excitation and inhibition that ends during mid-gestation and the early postnatal period. Many of these neurotransmitters originate in the brainstem and affect development of the whole brain including cortical maturation.

Early gestation

Noradrenaline, the best marker of arousal and sympathetic activity, is concentrated in cells in the brainstem as early as five weeks of gestation, especially in the locus coeruleus within the caudal pons. Five major adrenergic tracts originate in the brainstem and innervate the whole brain. Adrenergic activity is among the strongest to initiate cell migration to the cortex and cortical neurogenesis (96). At early gestation the excitatory brain activity is based on noradrenergic (96) and cholinergic pathways (97) up to the stage of brainstem integrated development. Developmental studies showing a correlation between acetylcholine receptor expression and the peak in AChE activity during periods of myelination, suggest

ACh signaling as a mechanism for functional activity in the axon to stimulate myelination early in pregnancy (98).

During this early stage of gestation, the heart is among the first organs to develop, undergoing proliferation and differentiation through 10 weeks GA with increasing heart rate over time (99,100). The functionality of the heart measured by heart rate, heart rate variability and vagal tone using ultrasonic tools during embryonic life is shown to correspond to neurobehavioral measures such as behavioral states and motor movements (99). Heart rate variability and neurobehavioral measures develop in similar trajectories (101). Maturational changes in the innervation of sympathetic and parasympathetic autonomic processes (102)**,** including vagal myelination (103), and alterations to central mediation within the medulla oblongata and adjacent loci (104) are among the most well-documented neural components that contribute to amplification of heart rate variability over gestation.

Mid- to late-gestation

The parasympathetic system undergoes accelerated maturation at 25–30 weeks GA, a time period when premature newborns may already be *ex utero* and experiencing transition to the new environment (79,105,106). Specifically, the vagus, myelination of the vagus nerve starts at 24 weeks gestation (103), suggesting the same timing for changes in excitatory and inhibitory ends in the brainstem. Indeed, at this crucial timing, mid-gestation, ACh levels appear to be reduced and they turn to have an inhibitory role within the brainstem pathways (97). A further reduction is evident between fetal and adult stages. This is assessed by binding of muscarinic ACh receptors. In the developing brainstem, mAChRs localize to sites in which ACh via mAChR interactions have been shown in animal studies to influence regulatory and executive functions (107–111).

GABAergic cells are contained in 20-40% of all neural terminals. GABA is regarded as inhibitory in the human brain. However, during development it acts as a trophic factor that affects proliferation, migration, differentiation, synapse maturation and apoptosis (112,113). C1- channels switch from depolarization to hyperpolarization during mid-gestation resulting in switching the GABAergic activity from excitatory to inhibitory. The K-Cl co-transporter KCC2 plays multiple roles in the physiology of central neurons, including influencing the development of neuronal circuits and the dynamic control of GABA and glycine signaling.

GABA-releasing synapses appear before glutamatergic synapses (114). Glutamate transport is a primary mechanism for regulating extracellular levels of glutamate in the central nervous system (115). In animal models glutamate expression increased with age with a major reduction postnatally (115–117). Thus, the well-established excitatory role of glutamate is evident and glutamate levels increase from mid-gestation throughout fetal development at the late pregnancy stages, while the excitatory effects of ACh decrease.

White matter (WM) is responsible for inter-neuronal connections throughout the brain that are a driving force in cognitive development. The association between the development of WM in early life and maturation of brain functioning as detected by EEG has been reported earlier (27,118,119). In preterm infants born as early as mid-gestation, beyond the risk for destructive lesions, disruption of the normal developmental trajectory of cellular elements of the white and the gray matter occurs. In the acute phase, in response to hypoxia–ischemia and/or infection and inflammation, multifocal areas of necrosis within the periventricular white matter involve all cellular elements. White matter injury, recognized as a major global health issue, is a well-known adverse outcome of extreme prematurity that disrupts the normal development of myelination (120). The period from 23 to 32 weeks gestation constitutes the highest risk for white matter injury, and dysmaturation of WM (121) with a peak at 28 weeks' gestation (122).

Thus, this time window validated in healthy fetuses, appears to be a critical period in brain development. Specifically, MRI DTI studies focusing on the end of the second trimester, reported that for all tracts, the volume and FA increased, and the ADC decreased with GA (123,124). The complex network of structural connections that arise in this period shape functional connectivity and higher order neurocognitive functions for the life span of an individual (125,126). Therefore, the same time window of critical development from mid-gestation onwards is suggested for neurogenesis of WM and myelination as well as for the changes in biochemical inhibitory and excitatory terminals as well as a risky period for preterm infants.

The GABAergic neuronal density increases in the cortex over late gestation, also with a peak at term (127). The second half of gestation is a period of rapid development of the cortical GABAergic system that continues into early infancy (114). During this time window of mid to late gestation, starting at 26 weeks GA and maturing at 38 weeks GA, the association between neurobehavioral measures and heart rate becomes more pronounced. Fetuses respond to stimulation, as measured by these two levels of functionality (99,128). Vagal tone then becomes the main representation of the progressing maturation of ANS coupling with the developing cortex (129). During this time window, these two levels become

sensitive to circadian rhythms (130) and demonstrate two facets of the pathways towards maturation of the multiple system synchronicities described here as well as the chronological aspect of self-regulation development as suggested in this paper.

Birth and postnatal period

Cortical regulation of the brainstem and coupling of the ANS with the cortex can be detected in changes in EEG waves from birth through early childhood. To continue the description of ANS synchrony developmental milestones beyond gestation, we will detail the main developmental pathways of the EEG waves that were found to be related to the emerging executive functions.

The EEG alpha wave associated with memory retrieval and attention regulation develops postnatally to frequencies of 10Hz up to the age of 3 years and continues to develop through adolescence along with cortex maturation, especially regarding accumulation of white matter in frontal lobes (76). The growth of volume and synaptic organization is seemingly accompanied by important changes of alpha activity in primary visual areas and crucial changes in the frontal areas (76,131,132).

In term born infants less than 2 months of age, periods of quiet sleep (or quiescence) are characterized by repetitive bursts of high-voltage slow wave electrical activity alternating with attenuated 3 Hz mixed-frequency activity. This characteristic pattern is known as Trace´-alternant (TA) (133,134). TA is defined with 3-8s bursts of high amplitude slow waves separated by 4-10s low voltage mixed EEG (theta with some delta alpha and beta). This pattern disappears by 46-48 weeks GA and a more continuous sleep pattern appears during quiet sleep associated with higher heart rate variability (135).

Thus, the baseline EEG in newborn preterm infants, measured with minimal or maximal number of electrodes and channels is discontinuous. This pattern is characterized by bursts of high amplitude delta–theta activity (sometimes superimposed with faster activity) intermixed with periods of quiescence (interburst intervals – IBIs). With maturation of normal inhibitory GABAergic transmission, spontaneous events are gradually abolished and ‘continuous’ oscillations emerge at different frequencies due to the increasing influence of exogenous sensory driven input. Consequently, the overall amount of discontinuity decreases and continuity increases with GA. The EEG pattern that develops in the most immature newborns from 23-24 weeks through 40 weeks GA has four major trends: (i) increasing continuity, with defined periods of EEG quiescence for specific GAs, (ii) the appearance of sleep cycling, (iii) advances in synchrony between hemispheres, (iv) and the disappearance of several transient waveforms of prematurity (136).

The development of quiet sleep in the newborn is influenced by lack of exposure to the maternal circadian rhythms' and to maternal melatonin crossing the placenta (18,32,84). Note that this event is of vast importance for the development of quiet alert awake state. The consolidation of quiet alertness is associated with prolonged incidences of quiet alert state. Alert state is associated with better cognitive functioning and self-regulation, which in turn reflect parasympathetic-sympathetic in-concert activity (18,32). A further development in sleep organization characterized by increased slow waves and spindle activity during quiet sleep and coupling with circadian rhythm takes place during the first 6 months of life in both term and preterm infants (130)

Sleep and wakefulness patterns mature through the inhibitory function of the post synaptic GABAergic and cholinergic neuro-activity which interact to regulate the levels of excitatory norepinephrine and glutamate (137–140). Inputs from the brainstem are modulated by the reticular formation, thalamus and the preoptic area of the hypothalamus on their pathways to the cortical circuits. GABAergic neurons are responsible for the timely impact on the hippocampal theta wave which characterizes early development, while cholinergic neurons are the pacemakers of the amplitude. In turn, glutamate acts as an excitatory end on the GABAergic and cholinergic neurons' inhibitory function to support hippocampal theta rhythm. In addition, the number of spikes in a burst and the interburst frequency (2–14 Hz) are dependent on a consecutive regression in the brainstem cholinergic input (137–140). Thus, the development of the continuous EEG patterns and especially, that of the first alpha and then the beta emergence from the theta-delta wave, promoting increasing low voltage fast activity of wakefulness and executive cortical functions, represents the development of the ANS synchrony that underlies the self-regulation clock. The emergence of brain synchronicity is in fact represented by the increased balance between excitatory and inhibitory terminals and developmental changes in the targeted receptors as well as mutual regulation between subcortical and cortical regions beyond the structural volumetric development.

Furthermore, KCC2 is expressed around birth in the brainstem and then a week or two postnatally in the hippocampus and thereafter in the cortex (141,142). Thus GABA is excitatory on immature neurons and has a trophic effect on cortical development. At least 20% of GABAergic neurons in the white matter migrate toward the cortex over late gestation. After term, migration declines and ends within 6 postnatal months (127).

The interchange between the excitatory sources, meaning shifting from excitatory acetylcholine and GABA activity to glutamatergic excitatory expression that becomes more dominant late in gestation,

468 occurs within the time window of mid-gestation. This is also the time window for the GABA turnover to
469 inhibitory function and for the start of vagal myelination towards brainstem maturation (98,127,143).

470 The regulated interchange between peaks of ACh and glutamate activity postnatally at ages of mid-
471 gestation to term may affect the developmental path of neural cell migration from the brainstem to the
472 cortex (96) in term born infants. In addition, in term infants, GABAergic granular neurons balance against
473 excitatory (glutamatergic) pyramidal neurons that are required for cognitive processing. This involves
474 modulation of excitatory events by inhibitory neurons, as well as a coordinated balance between
475 excitation and inhibition maintained over a large range for many stimuli. This process may be
476 dysregulated in preterm infants and point to this period early in life as a precarious passage to later
477 developmental achievements for preterm infant .

478 Dysregulation in the peak interchange junction between excitatory and inhibitory neurotransmitters (96)
479 may be the reason for the reduced/aberrant myelination of the vagus nerve in preterm infants exposed to
480 the extra-uterine environment before term. As myelination precedes axonal growth while supporting the
481 increase in white matter (144) the progress in myelination may play a crucial role in balancing the
482 initiation of neural cell migration from early to late developing region, thus supporting the emergence of
483 executive functions in the neonate.

484 Furthermore, as GABA receptors are prominent postnatally and during early childhood over glycine
485 receptors, the relatively stressful conditions in the NICU may impose suppression on the GABAergic
486 shift from excitatory to inhibitory expression and its interactions with glutamatergic functions thus
487 further affecting vagal myelination. These conditions in the NICU may also create an overload on the
488 immature vagus nerve by causing sympathetic and parasympathetic compromises as shown in prolonged
489 flaccid and over aroused states (12,16,37). Therefore, ANS synchrony may be initiated by the timely
490 molecular changes affecting myelination. This also points to the relevance of ANS supporting
491 interventions during this period.

492 The brain-heart connection is a Darwinistic proposition (145). Indeed, the brain is connected to cardiac
493 myocytes and arteriolar smooth muscle cells, which are the cardiovascular autonomic effectors, by di-
494 synaptic neuronal connections of the preganglionic and ganglionic autonomic neurons (146). It has been
495 suggested (147) that the expression of thalamo-cortical neurons, skeletal muscles, and the ANS, which
496 explain the EEG, electromyographic, and cardiovascular features are modulated and controlled by
497 circuits in the brainstem (148). The cortical-ANS coupling may reflect the common dependence of EEG
498 and HRV (the vagus activity measurement) variables on the activity of brainstem circuits. The brainstem

appears critical in this respect, as key neural elements of autonomic, respiratory, and cardiovascular control are developing within the medulla, pons, and midbrain (147), together with key elements of the stepwise progressive neuronal connectivity that control EEG activity through the thalamus and basal forebrain (148).

The brainstem regulates cortical development in a bottom-up top-down manner within afferent and efferent pathways (149,150). It also regulates the ANS coupling with the developing cortex (1).

Vagal myelination progresses with age through the first months of postnatal life (151). Developing cortical regions regulate the continuation of brainstem control of vagus myelination through the first months of life (8). It has been argued that the vagal pulse represents the coupling of the heart with brain regions such as the medulla and frontocortical areas and that social interaction in early life is crucially supported by vagal myelination (100,101). These observations may be extended to explain the emergence of executive functions beyond emotional-social regulation as originally suggested since initiation and modulation of social reactions are dependent on the availability of germinal executive capacities. However, although the progress of vagal myelination is part of fetal development, these observations do not include embryonic spatiotemporal considerations nor a time scale of multi-system development as proposed in this paper. In this paper, using a multi-system perspective, we add the embryonic phase to postnatal description of brainstem-cortex coupling, emphasizing the full spectrum of vagal progressive stages as its myelination rhythms are anatomically and biochemically reliant on- and conditional to-brainstem development.

The preparatory self-regulation phase

The changes in inhibitory and excitatory terminals during gestation from early to late stages are programmed in a stepwise timely manner, suggesting a clock for the maturation of ANS synchrony with a significant time window of massive changes at mid-gestation. In this regard, the prenatal advancing neurotransmitter interchange in the developing brain is suggested as a preparation of the fetus towards self-regulation in the extra-uterine environment. We term this preparatory phase as the "self-regulation clock" to be further developed after birth. We described the prenatal milestones of the development of this clock and emphasize that interference within the uterine environment may have critical impact on further development of self-regulation milestones after birth [Figure 4].

With advanced cortical development, the cortex has greater control over the brainstem in direct (e.g. corticobulbar) and indirect (e.g. corticoreticular) pathways emerging in the motor cortex and ending in the source nuclei of the myelinated motor fibers that develop towards and from the brainstem (152,153). This occurs at the end of healthy pregnancies through early childhood.

The self-regulation clock

The self-regulatory clock milestones are viewed in this manuscript as the development of the synchrony between the sympathetic and parasympathetic systems and the developing control of the cortex over the brainstem with major implications for the emergence of germinal executive functions in the infant as the fundamentals of later to be developed goal-directed behaviors . We suggest that the development of regulatory functions follows a genetic clock with specific rhythms and time windows for each developmental acquisition prenatally and postnatally. At early gestation the majority of the developmental processes that the embryo undergoes, both cellular and chemical, depend on sympathetic activity. By mid-gestation the acetylcholine declines and the excitatory tone in the fetal brain turns to be dependent on glutamate; GABA turns to be inhibitory and not excitatory as earlier, and myelination of the vagus begins. This seems to be the time window for the generation of self-regulatory functions through the developing synchrony between the sympathetic and the parasympathetic systems. In preterm infants who may already be exposed to the out-uterine environment at this stage, many of the supportive means for the self-regulatory clock are dependent on the match-mismatch (154) ratio between the preterm newborn ANS condition and the given environment. As the NICU environment is stressful (155) for the immature brain, the stress reaction of the preterm infant and his/her immature hypothalamus (including release of glucocorticoids and the HPA axis function) may induce a delay in the maturation of all diurnal clocks (156–158) including the ontogenetic clock of ANS synchrony, thus delaying the development of self-regulatory functions (159). Supportive environments that aim at reduction of stress may shorten this delay (27). Postnatally, the regulation of survival behaviors such as secure attachment bonding, regular breathing and on demand oral feeding (160), are the key windows for the acquisition of self-regulatory functions. Another key element that can be supported by environmental facilitation is the consolidation of quiet sleep and the development of alpha waves, both related to states offering optimal functions of age-dependent executive functions (93). We suggest that the self-regulatory clock is genetically programmed at an early gestational stage to reach the status of ANS synchrony. The dialogue of the growing infant with the environment by match-mismatch trajectories (154) may shape this clock up to the age of two years by which time the cortical-brainstem circuits should be established. Stress and

disease may delay this accomplishment as multiple requirements are imposed on the organism with limited conditions for achievement of the clock trajectories aimed at synchronous functioning. The synchronous ANS maturation depends on the maturation of the CST and the transition of control on self-regulatory functions from the brainstem to the cortex. As the CST is involved in transferring the control over to the brainstem as well as in the maintenance of ANS synchrony we suggest that the ontogenetic developing function of the self-regulation clock may be defined as the measurable ratio between the maintained balance within biochemical secretion of neurotransmitters and the gradients of CST volume development. We further suggest that beyond the ontogenetic clock of self-regulation, a specific sleep-wake circadian clock is among the functions of the CST affecting the availability of infant self-regulation by maintaining the coupling of the ANS with the cortex. Whereas global WM intact and undamaged development is required for the emergence of optimal cognitive capacities in the newborn and preterm infant, we propose that the clock described here is an a-priori condition for these anticipated uncompromised executive functions and that this clock consolidation precedes the emergence of these functions.

Location of the self-regulation clock

As both the sympathetic and parasympathetic systems originate in the brainstem and ANS synchrony is dependent on cortical-brainstem connectivity as well as on the developing control of the cortex over the brainstem, the self-regulation clock which is dependent on ANS synchrony, is suggested to be located in the corticospinal tract (CST). This developing structure which is the basis for the maturation of cortical control over the brainstem is responsible for cortex-brainstem connectivity (Figure 5). The CST is one of the pyramidal tracts. It is the largest connection between the cortex and brainstem; a white matter pathway starting at the cerebral cortex that terminates on lower motor neurons and interneurons in the spinal cord. Corticospinal tracts undergo earlier maturation than other tracts (as measured by fractional anisotropy) but slower volumetric growth, while the anterior to posterior gradient in white matter microstructure development found the posterior forceps developing at a faster rate than the anterior forceps minor between mid-gestation and two years of age (161). This has implications for the time window for the development of cortical control over the brainstem, suggested as starting at mid-gestation and undergoing a long process up to two years of age. Morphological studies demonstrated that corticospinal axons reach the lower cervical spinal cord by 24 weeks GA at the latest. After a few weeks, they progressively innervate the grey matter such that there is extensive innervation of spinal neurons, including motor neurons, prior to birth. Functional monosynaptic corticomotoneuronal projections were demonstrated neurophysiologically from term, but are also likely to be present from as early as 26 weeks

GA. (162). After leaving the neocortex, CST axons form bundles and run through the internal capsule and cerebral peduncles before reaching the brainstem in a ventral position. CST axons maintain their ventral position (forming the pyramids) until they reach the caudal part of the medulla. At the junction between the brainstem and spinal cord, the vast majority of CST axons cross the midline and pass from a ventral to a dorsal position, forming the pyramidal decussation, before continuing their trajectory in the contralateral spinal cord (163,164). The termination pattern of CST axons in the spinal gray matter depends on the cortical territory from which they originate, further stressing the different roles of this pathway (164).

Although the cortical plate is barely formed by 7 weeks GA, the CST axons reach the medulla by that time. These axons reach as far as the lumbar enlargement by 18 weeks GA and thereafter, the lower cervical spinal cord by 24 weeks GA. Following a waiting period of a few weeks they progressively innervate the grey matter with a peak of the prolonged myelination progress at 40 weeks GA. Synaptic projections of the CST are established during the third trimester of pregnancy. It has been suggested that rather than furthering motor control, this massive development is aimed at coupling with the cortex and cortical development. Longitudinal and cross-sectional studies of normal babies and children report neurophysiological findings that are consistent with withdrawal in significant numbers of corticospinal axons over the first 24 postnatal months (165) which provides evidence for continuous CST development up to 2 years of age (166). The final pattern of the origin and termination of the CST is shaped during development by the balance between projection and withdrawal of axons (167). The time window for prenatal and postnatal CST development coincides with the same timing of massive fetal and newborn development, described here as the basis for the developing clock of self-regulation. This suggests that its myelination represents the chrono-progression of ANS coupling with the cortex through the brainstem.

Regarding development of preterm infants, CST microstructural properties (FA, MD) differ significantly between adults born prematurely at a very low birth weight vs. those born full term (168) and between 8yr old children born prematurely at a very low birth weight vs those born full term (169).

As mentioned earlier, the CST is historically known for its role in motor functioning. However, our suggestion that it is a mechanism underlying early self-regulation and a basis for later development of executive functions builds upon earlier evidence-based views and assessments such as the very early after birth assessment by Prechtl (170). A more recent observation which includes embryonic MRI motor observations is the Fetal Finger Index (171) (a motor observation method which precedes later

developing communicative functions) (172). We add to this body of knowledge that beyond its traditional role in motor development, the CST has been recently shown to be involved in the developing self-regulation towards future executive functions in preterm infants. Indeed, it was shown to be associated with goal directed upper limb movement segmentation in 8yr old preterm born children (173). In addition, studies from other groups found correlations with reading and language functions in the CST, in children and adolescents born prematurely (174,175). Interestingly, In healthy children, the CST was found to be associated with reading performance (176).

This view is consistent with Kostovic's suggestion (87,177–179) that executive functions, termed as "goal-directed behaviors", emerge later during childhood and they are based on earlier fetal development of the thalamic fibers' penetration of the cortical subplate at mid-gestation (52). We suggest that the maturational process of these behaviors is dependent on development of cortico-thalamic-brainstem connections. The ontogeny of these connections during fetal life determines an integrative control of behaviors and the foundation of control over the progression from reflexive behaviors and transient synapses to solid reactive and self-initiated capacities later in childhood, developing into more and more differentiated reactions and goal directed behaviors from the seeds of excitation-inhibition balance acquisition. The crucial role of the CST in these cortico-thalamic-brainstem connections has been demonstrated in preterm infants, showing that injury to the CST precedes reduction in thalamic volume (180). This suggests existing pathways between the CST and the cortico-thalamic interconnectivity reported earlier but however without regional specificity (181). This implies that the sophistication of executive functions later in childhood depends on the transition of control over fetal excitation-inhibition development from the brainstem to the thalamus, two major gateways of sensorimotor information, but also suggests that these two subcortical regions involved in early control, need to work in concert and with competing signals to and from the immature cortex for the progression of normal development. As cortical control may need to rely on excitation-inhibition balance in these subcortical regions, the cortical selection between competing signals governs the final behavioral output. In this regard, as we noted earlier, self-regulation is a behavioral term which parallels the neurological term excitation-inhibition balance described in this review. The transition from reactive and spontaneous behaviors of the fetus and newborn to the goal-directed executive functions of the child is therefore dependent on early development of the CST and its impact on the thalamic projections to the cortex.

The early development of the CST during gestation and the corresponding neurogenesis progression with a mandatory crucial role in the developing control of the cortex over the brainstem and in ANS functionality maturation, suggests that this tract's time window for development is vital for WM normal development and resulting neurobehavioral parameters such as self-regulation. To support this view, others found excitation of the CST in response to environmental stimuli (182,183) implying that this sensitivity of the CST may have a possible role in the developing self-regulation which is known to be dependent on both the infant's available neural connectivity and the imposed and perceived environmental input (27,184). The prediction of executive functions by self-regulation is widely known (e.g. Ferber et al., 2011). Thus, we suggest that the CST is affecting the quality and emergence of executive functions in the human newborn as a source of modulatory self-regulation.

Taken together, the ratio between the neurotransmitters' interchange and the role of CST in cortex maturation through the impacts of developing control of the cortex over the brainstem while the brainstem generates the synchronization within the ANS, suggests that an independent ontogenetic clock of self-regulation is seated in CST function and develops in a stepwise ontogenetic manner with direct and indirect effects on the emergence of executive functions later in childhood, and that this clock is sensitive to the balance between neurotransmitters and levels of synaptic storage during gestation and especially after early birth.

Testable hypotheses for further research:

As a starting point of a research endeavor, the association between the volume (and function) of the CST and the scores in self-regulation tests such as the Assessment of Preterm Infants' Behavior (ABIP), The Brazelton test and the Prechtl General Movements Assessments should be tested to critically examine the hypothesis that self-regulation is part of (or at least strongly associated with) the CST functions. Further steps in research may need to follow up various stages of the CST development with imaging and the Fetal Finger Index**,** which has been shown to predict neurobehavioral outcomes after birth (172)**.** On the molecular level, self-regulation, described by a balanced ratio between acetylcholine and cortisol, should be correlated with CST volume and function. At an advanced stage, investigating whether interventions in NICUs that promote self-regulation within the window of opportunities detailed in this paper, will increase the volume of the CST and its connectivity as outcome measures. In addition, preterm infants who suffer from asphyxia during the window of opportunities for the maturation of the CST as detailed in this paper, could be tested for size and connectivity of the CST as well as for the association of CST connectivity with the CA+K+ pump known to collapse during asphyxia (185).

Conclusions

The concept of self-regulation has been postulated to underlie later developmental achievement of the infant including executive functions. This concept has not been related to an overarching outline of ANS synchrony and its developmental pathway from fetal life to early childhood as yet. Self-regulation has been mostly measured behaviorally. We suggest that ANS synchrony, represents the biological basis for the developing self-regulatory functions and we term it the self-regulation clock. This is the first review to propose a developmental process of the ANS, which seeks balance and is suggested as a prerequisite for the emergence of future executive functions. Preterm infants who lack this balance show compromise and delays in the emergence of executive functions. The synchronization between the two branches of the ANS is sensitive to internal tonic and phasic crosstalk and to external level of input. We suggest that the key role of ANS maturation and especially its impact on the emergence of executive function follows a stepwise ontogenetic clock. This clock is apparent in neurotransmitter interchange, WM development and maturation of EEG patterns. Multiple types of data show accumulating evidence of the time windows of this stepwise process emphasizing the association between optimal development and optimal outcome. The initiation of the self-regulation clock early during gestation is continued in a complex multi-level progression in an excitation-inhibition manner. It starts from early brainstem development, its role in the development of the sympathetic and parasympathetic systems and progresses to a complex development of cortical control over the brainstem through the largest connection pathway, the CST, which in turn recruits the developing midbrain and its connections with the limbic and nigrostriatal regions for the achievement of ANS synchrony following the penetration of thalamic fibers in the waiting zone of the subcortical plate. We suggest that the stepwise process of the emerging synchronization within the ANS is centrally located in the CST and term it as the self-regulation clock. Recent studies show the involvement of the CST in executive function in infants born at term as well as in those born prematurely. The processes described in this review progress from early gestation up to two years postnatally. Our review paves the way towards important hypotheses and studies on the self-regulation clock, which is central to normal development and comprises the time windows for interventions to promote the neurobehavioral functions of preterm infants.

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Figure captions

Figure 1: The interplay between the neurobehavioral subsystems through excitation-inhibition of each other while faced with environmental inputs and return to balance following achievement of a developmental task.

Figure 2: A step-response acquisition of a developmental task running from zero (pre acquisition status) to one (acquired capacity, e.g. the first breath, the first step, the first word).

Figure 3: The dysregulation and lack of synchrony in ANS functioning of the preterm infant compared to the optimal range.

Figure 4: The stepwise developmental progress of the self-regulation clock from conception to postnatal life.

Figure 5: The origin of cortical control over the brainstem by which the CST develops to become the location of the self-regulation clock.

Figure 1.TIF

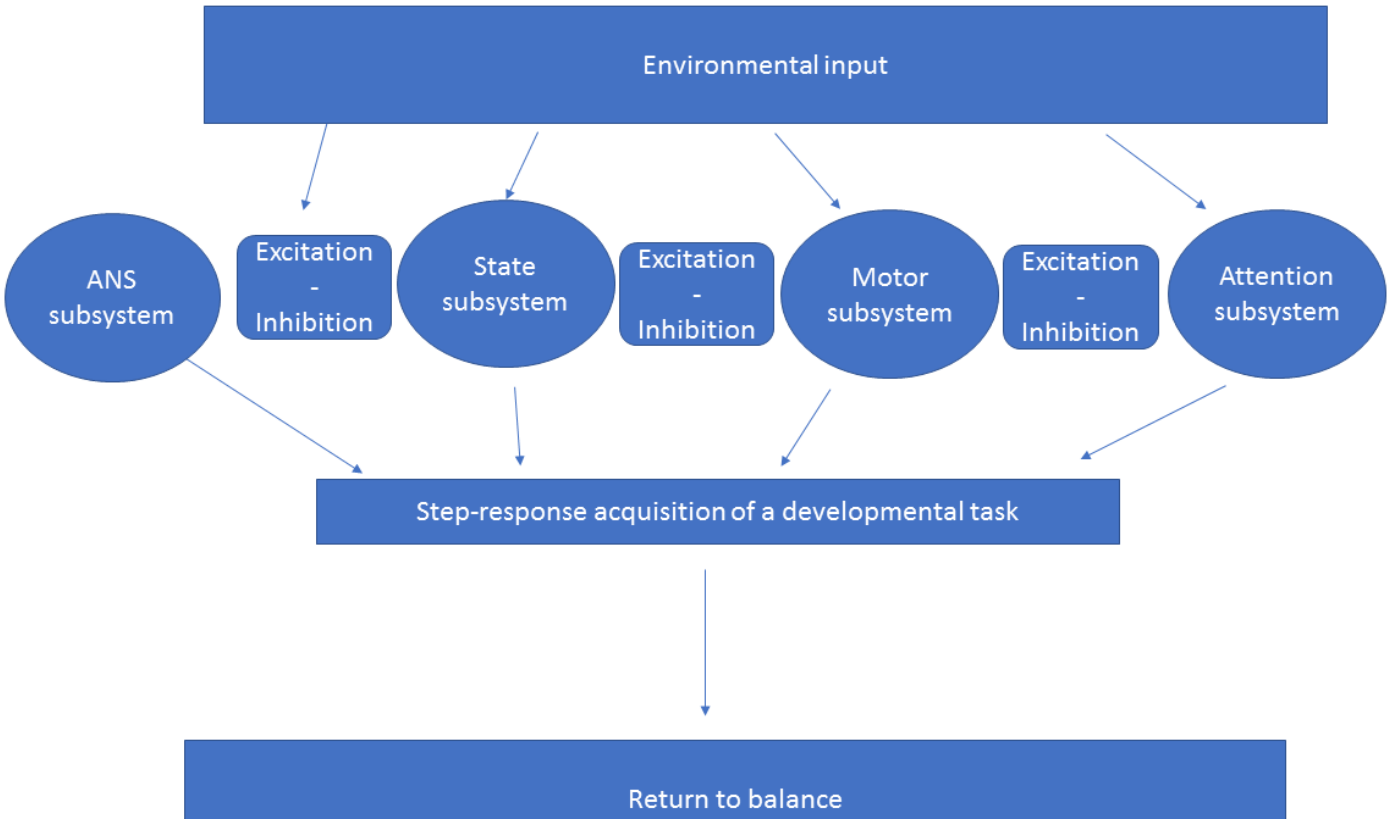
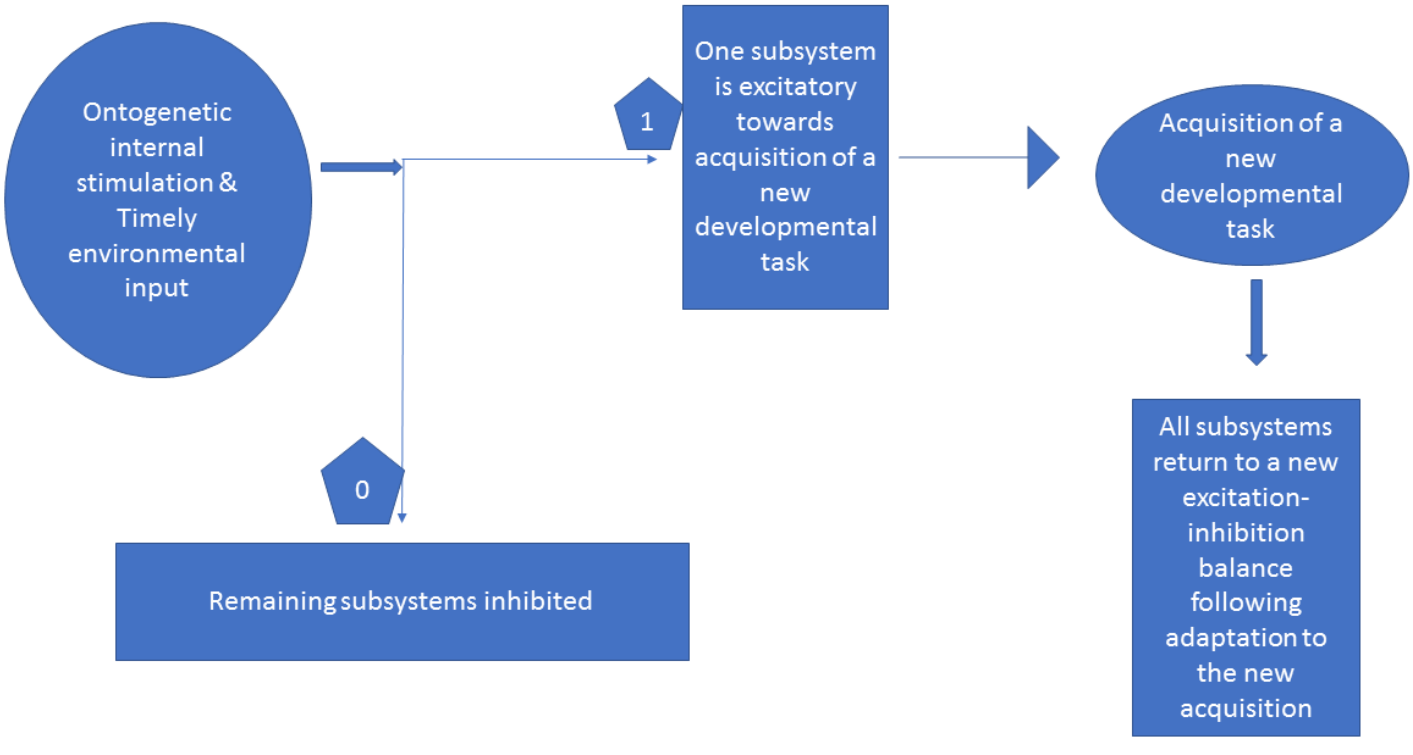


Figure 2.TIF



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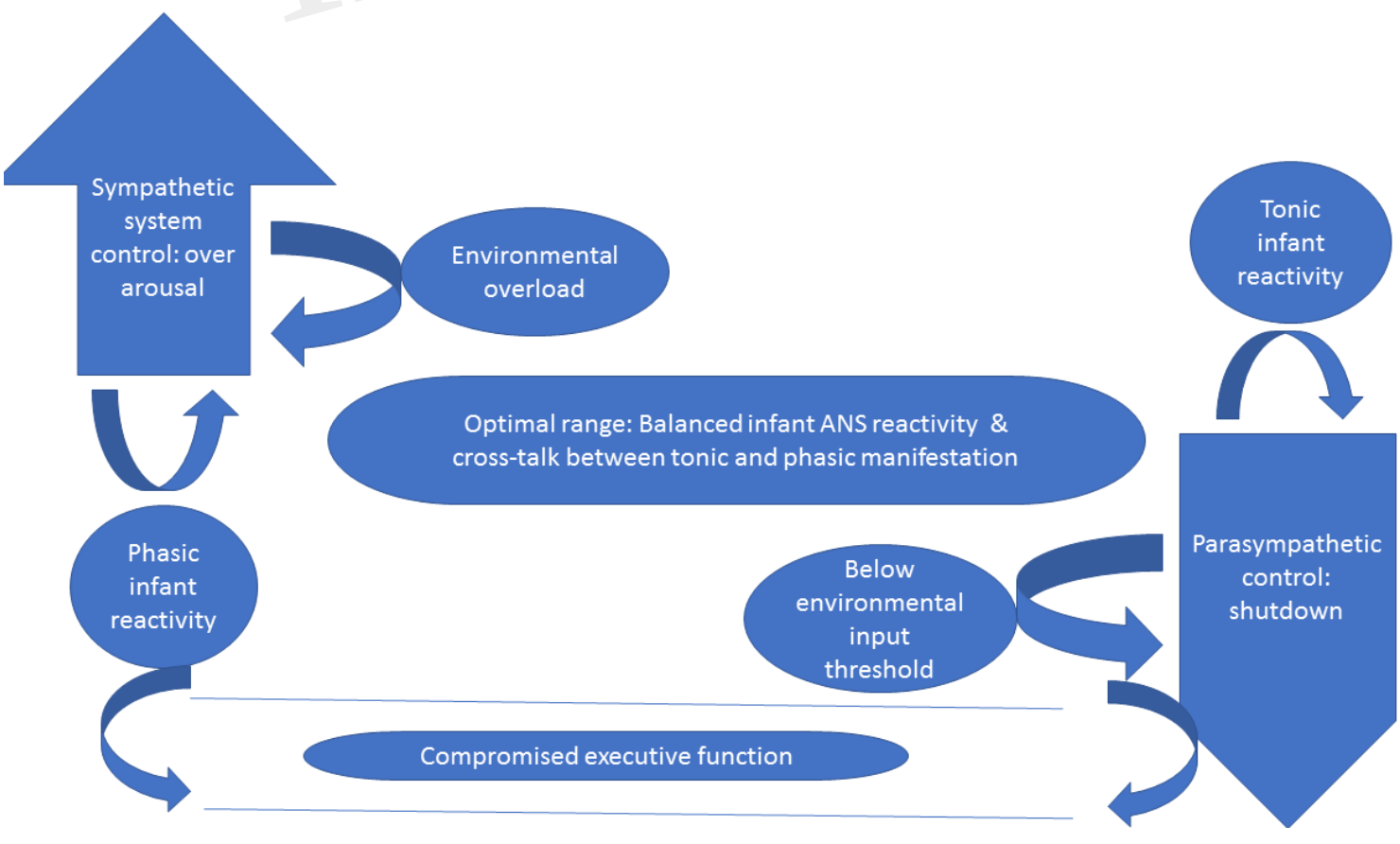

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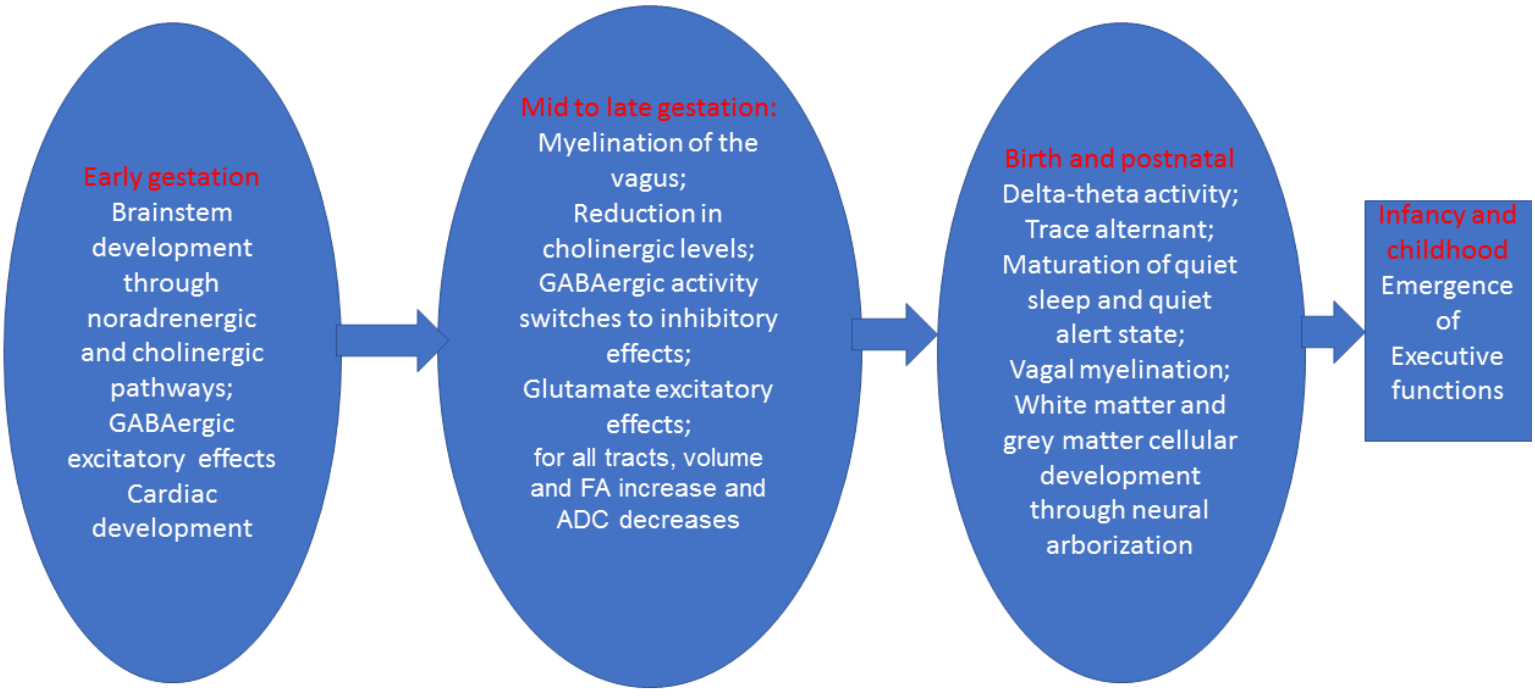

Figure 5.TIF