THE JOURNAL OF
CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH
Journal of Child Psychology and Psychiatry 49:10 (2008), pp 1031–1041 doi:10.1111/j.1469-7610.2008.01918.x

A neurobiological model for the effects of early brainstem functioning on the development of behavior and emotion regulation in infants: implications for prenatal and perinatal risk

Ronny Geva and Ruth Feldman
The Gonda Goldschmied Brain Research Center, Bar Ilan University, Ramat Gan, Israel

Neurobiological models propose an evolutionary, vertical-integrative perspective on emotion and behavior regulation, which postulates that regulatory functions are processed along three core brain systems: the brainstem, limbic, and cortical systems. To date, few developmental studies applied these models to research on prenatal and perinatal risk. We propose a conceptual model that incorporates three integrated levels of observations for the study of early risk: (a) brainstem-related physiological regulation of cyclic processes and sensory integration, e.g., vagal regulation, circadian rhythms; (b) emotion and attention regulation capacities that draw on the integration of brainstem and limbic systems; and (c) higher-level outcomes that draw on the intactness of brainstem and limbic networks, including socio-emotional self-regulation, inhibitory control, and cognitive processing. We discuss implications of the model for the development of regulatory capacities during the prenatal and early postnatal stages in infants born with specific perinatal risk. We underscore the importance of assessing sub-cortical and brainstem systems and the longitudinal effects of transitory brainstem dysfunction on physiological homeostasis, motivation, arousal-modulated attention, stress reactivity, and mother-infant co-regulation. The assessment of brainstem dysfunction can be conducted during hospitalization and may help detect infants at risk for the development of self-regulatory deficits at the first weeks of life. **Keywords:** Audiology, brain development, emotion regulation, executive function, perinatal, prematurity. **Abbreviations:** ABR: auditory brainstem evoked responses; IVH: intraventricular hemorrhage; MRI: magnetic resonance imaging; CBSF: compromised brainstem functioning; VT: vagal-tone; AMA: arousal-modulated attention; CCK: cholecyctokinin; CNS: central nervous system; US: cranial ultra-sound; NICU: neonatal intensive care unit.

Neurobiological models of emotions propose an evolutionary, vertical-integrative view on emotion and behavior regulation (Panksepp, 2005; Tucker, Luu, & Derryberry, 2005). Regulatory functions are theorized to be processed along three core brain systems: the brainstem, limbic, and cortical systems, which are integrated into a vertical-integrative hierarchical system. This developing system draws upon brainstem-related homeostatic systems, which provide the physiological foundation for the regulation of state, attention, and emotional reactivity. Brainstem-mediated systems, in turn, enable the development of arousal, attention, and emotional regulation that drive high-order self-regulatory abilities, effortful control, and socio-cognitive processes. This integrated system is based upon brainstem relay, which undergoes a rapid developmental maturation during the last quarter of gestation. Optimal development of the vertical-integrative system depends on the provision of specifically-tailored environmental and maternal stimulation. As such, infants born at pre- and perinatal risk are at a greater risk for specific developmental disruptions of this system.

To date, knowledge on the hierarchical functioning of the brain is based primarily on animal research. However, electrophysiological, biochemical, imaging, and behavioral data may be pulled together to examine the implications of these models for the development of behavior and emotion regulation during the very first phases of postnatal life in infants born prematurely or with perinatal risk. Incorporating development into the model may increase empirical attention to the functioning of brainstem systems as predictors for the development of regulatory capacities in high-risk neonates.

Evidence for the vertical-integrative perspective comes from neurochemical, imaging, electrophysiological, and clinical studies, mostly with adults. Neurochemical systems, including the serotonergic, dopaminergic, noradrenergic, and other neuropeptidergic systems, involve hierarchical and synchronous functioning at brainstem, limbic, and cortical levels (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Damasio et al., 2000; Jentsch, Roth, & Taylor,

Conflict of interest statement: No conflicts declared.

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

2000; Gunnar & Quevedo, 2007). Such vertical integration of neurochemical systems also affects emotion regulation in infants and toddlers (Rothbart & Rueda, 2005). The noradrenergic system, for instance, has been shown to mediate arousal regulation in social contexts, such as mother–infant interactions, through a brainstem–limbic–right-hemisphere brain circuitry (Tucker et al., 2005; Schore, 1997) and fight-or-flight reactions to stress (Morilak et al., 2005). Specific dopaminergic and serotonergic genes were found to mediate the effortful control dimension of temperament. This dimension, which involves prefrontal activity, emerges on the basis of brainstem–limbic-related functions: the surgency/extroversion component and the negative affectivity component (Rothbart, Sheese, & Posner, 2007; Posner, Rothbart, & Sheese, 2007).

Imaging studies of human adults similarly point to brainstem–cortical links in the processing and regulation of emotions. For example, Damasio and colleagues (2000) demonstrated the role of the brainstem in the perception, experience, and memory of self-relevant emotions. Although little imaging research is available in neonates, behavioral studies show that deficits in neonatal sub-cortical systems are related to later difficulties of attention organization and inhibitory control (Gardner, Karmel, & Flory, 2003; Karmel, Gardner, & Freedland, 1996; Geva, 1995). More specifically, neonates with brainstem dysfunctions showed poorer attention regulation as a function of arousal states at 1 month of age (Gardner et al., 2003); poorer attentional responses that were hyperresponsive to increased endogenous arousal at 4 months (Karmel et al., 1996); and less regulated inhibitory control on rapid automatized naming tasks at 3 years of age (Geva, 1995; Geva, Gardner, & Karmel, 2004). This line of work is also complemented by basic science research and animal decortication models which highlight the role of brainstem structures in integrating sensations from the environment with one's immediate goals and feelings in order to guide behavior and enable conscious awareness (Merker, 2007). These studies also indicate that higher-level capacities, such as executive functioning, self-regulation, and representational thought, which most likely involve cortical activity, also require simultaneous processing at the brainstem and limbic levels. Thus, brainstem-related systems are likely to play an important role in self-regulation. Taking this notion a step further, we propose that *prenatal disruptions in brainstem-related developmental processes are likely to impact on the development of self-regulation across childhood and beyond.* Furthermore, since brainstem structures mature early and precede the development of limbic and cortical structures, *disrupted development of brainstem structures and their functions in preterm and high-risk infants may serve as an indicator of later neuro-functional deficits*.

Effects of prenatal and perinatal risk on brainstem functions

During late gestation, at 33–38 weeks, there are significant developmental changes in the brainstem (Darnall, Ariagno, & Kinney, 2006). At this phase, various prenatal and perinatal risk factors affect brainstem functions and physiological homeostatic regulation of the heart and lung as well as the regulation of state and satiety (Darnall et al., 2006). Brainstem dysregulation may be indicated by anomalies in auditory brainstem evoked responses (ABR). Dynamical changes in latency of the three major ABR components correspond well to concurrent hypoxic-ischemic brainstem-related pathophysiological changes in neonates (Jiang, Yin, Shao, & Wilkinson, 2004). In large community studies, the risk for anomalies in ABR functions in neonates with various neurological impairments was substantially greater than among controls ($N = 1087$; Salamy & Eldredge, 1994). Similar ABR anomalies were found in preterm infants and in term infants with neurological impairments. Among premature infants at the Neonatal Intensive Care Unit (NICU), 16.1–28% of neonates failed the first ABR test ($N = 1613$; Galambos, Hicks, & Wilson, 1982; Murray, 1988). These studies highlight the susceptibility of preterm infants to brainstem dysfunctions.

Several studies have used ABR technology with groups of preterm infants or infants with *specific* perinatal risks. Brainstem dysfunction was found to be common in selected populations of preterm infants. Karmel and colleagues found functional brainstem dysfunctions in neonates with brain insult or with hydrocephalus ($N = 416$; Karmel, Gardner, Zappulla, Magnano, & Brown, 1988). ABR evaluations in neonates were found to be sensitive to perinatal asphyxia and hypoxic-ischemic damage in preterm infants (Jiang et al., 2004). Abnormal ABRs increased in cases of transient low Apgar scores even in the absence of chronic hypoxic-ischemic encephalopathy (Jiang, Xiu, Brosi, Shao, & Wilkinson, 2007) and in preterm infants diagnosed with chronic lung disease and bronchopulmonary dysplasia in the neonatal period (Wilkinson, Brosi, & Jiang, 2007). Such anomalies are diagnosed in young preterm infants at a critical period for the myelination of the equilibrium and auditory pathways in the brainstem, axonal sprouting, formation of central synaptic connections, improvement of synaptic efficiency, increase in axonal diameter, and development of central dendritic properties (Jiang, Brosi, & Wilkinson, 2006; Krumholz, Felix, Goldstein, & McKenzie, 1985; Moore, Perazzo, & Braun, 1995). Such poor

myelination of early-maturing brainstem structures in preterm infants points to the potential links between brainstem dysfunction and the risk for disruption in the vertical integration.

Relations between prenatal and perinatal risk and the development of the vertical-integrated framework

Specific prenatal and perinatal risks that interfere with myelination and synaptic functions in the brainstem may affect the development of adaptive self-regulation. Follow-ups of premature infants indicate relations between CNS problems and poor outcome (Hack et al., 1994; Jongmans, Mercuri, DeVries, Dubowitz, & Henderson, 1997). These studies, however, do not specify the neonatal CNS injury and rarely deal with the underlying mechanisms accounting for these deficits. In particular, little research has documented the contribution of brainstem structures to developmental psychopathology. Reliance on structural information or epidemiological factors alone may not be sufficient to detect subtle neuro-functional deficits that underpin self-regulatory capacities.

Recent studies have begun to address the evaluation of brainstem functioning in fetuses, neonates, and infants. These studies focus mainly on morphological changes or functional anomalies. Structural brainstem dysgenesis syndromes in fetuses, such as Pierre Rubin sequence, are rare and bear grave outcomes (Abadie, Morisseau-Durand, Beyler, Manach, & Couly, 2002; Roig et al., 2003). The symptoms are closely dependent on the excessiveness of the affected brainstem loci and are often related to orodigestive and cardiorespiratory anomalies (Abadie et al., 2002). In most cases of structural brainstem disorder, the cause is fetal vascular accidents (Roig et al., 2003). Other studies examined physiological brainstem dysfunctions in premature infants. Volpe (1995) pointed out that neuronal pathology can be detected at pontine levels of the brainstem in as many as 71% of the infants with intraventricular hemorrhage (IVH), and magnetic resonance imaging (MRI) studies indicated wider brainstem involvement than previously thought. Yet, very little information is available on the predicative utility of morphological brainstem MRI and ABR findings for the development of self-regulation in infants. It is important to note, however, that the sensitivity and specificity of ABR assessments were found to be significantly higher than those reported for MRI for the detection of sensory-neuro deficits (Valkama et al., 2001).

Model-driven hypothesis of neonatal brainstem dysfunction and developmental outcome

The proposed model (Figure 1) suggests both direct neurobiological and indirect behavioral long-term effects of compromised brainstem functioning (CBSF) on self-regulation. In line with the vertical perspective of neuro-functions, it is hypothesized that early brainstem trauma directly affects physiological regulation in the first weeks of life.

Physiological regulatory difficulties that reflect disturbed brainstem-mediated homeostasis may be evident in the following systems: (a) the autonomic nervous system as assessed, for example, by cardiac vagal-tone (VT; Porges, 1992) and by cardio-respiratory regulation (Hunt, 2006); (b) circadian regulation of arousal (Karlsson, Gall, Mohns, Seelke, & Blumberg, 2005); and (c) the modulation of

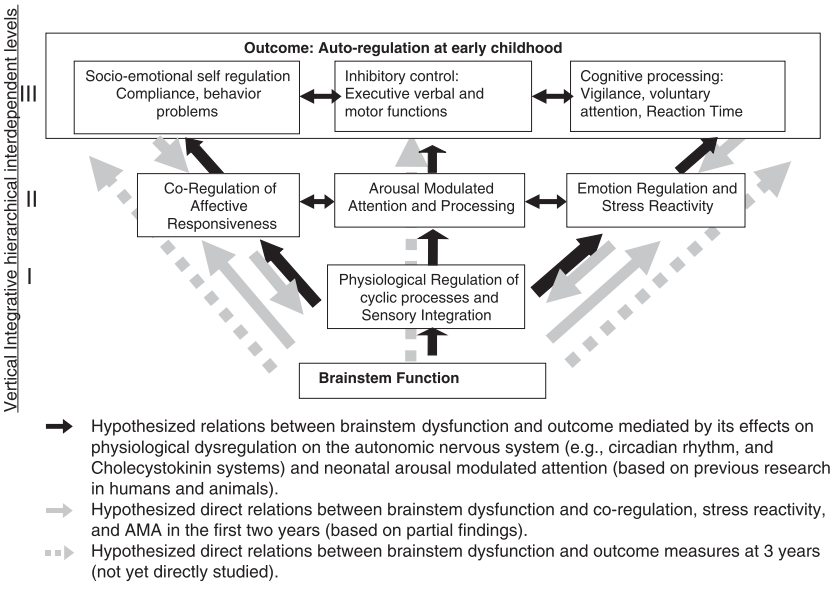

Figure 1 A schematic representation of the neurobiological model for the effects of early brainstem functioning on the development of behavior and emotion regulation in infants

visceral homeostasis of internal states, such as hunger and satiety (Batterham et al., 2007). These systems, which are mediated by the brainstem, were shown to interact with the development of emotion and attention regulation in infants (Porges, 1997). Consequently, the infant's ability to maintain proper physiological homeostasis in order to attend to external stimuli, to modulate arousal, and to react to stressful situations may be compromised.

Difficulties in the regulation of basic physiological functions such as sleep, feeding, or self-soothing may disrupt the management of negative emotions, the development of inhibitory control as expressed by conduct or antisocial problems, or lead to attention deficit or hyperactivity disorders at later stages. Several studies indicated that certain sub-groups of premature infants exhibit such symptoms more frequently than full-term infants, for instance infants diagnosed with intra-uterine growth restriction (Geva, Eshel, Leitner, Fattal-Valevski, & Harel, 2005) or very low birth weight infants with periventricular leucomalacia (Skranes et al., 2007). During later stages, maturation of top-down fronto-limbic connections, often in the right prefrontal cortex, is described as the apex of the proposed hierarchy (Schore, 1997) and enables adaptive coping responses to stress (Ellenbogen, Schwartzman, Stewart, & Walker, 2006). Accordingly, the development of higher functions, such as inhibitory control and social-emotional self-regulation, is hypothesized to be compromised (Dennis, 2006).

A developmental neuropsychological perspective on vertical-integration of brainstem dysfunction and the development of self-regulation

Brainstem trauma, as assessed by abnormal ABR and cranial ultrasound and/or MRI, typically resolves during the neonatal period (Wilkinson et al., 2007). Nevertheless, its physiological and behavioral consequences are identifiable in the neonatal period, provided one is searching for mechanisms that are mediated by brainstem functions. Mechanisms of arousal and attention are mediated by sub-cortical brainstem-related structures, especially prior to 2–3 months of age (Gardner & Karmel, 1995; Geva, Gardner, Karmel, Feldman, & Freedland, 1999a; Geva, Gardner, & Karmel, 1999b). Arousal influences not only tonic activity, but also gates specific sensory processing when internal or external factors are manipulated through feeding or stimulation (Geva et al., 1999a, 1999b). This self-limiting brainstem-related system helps neonates maintain homeostasis (Zeskind, Goff, & Marshall, 1991). Disruptions in the ability to shift arousal or maintain equilibrium impact on later cognitive, behavioral, and emotion-regulation capacities (Sigman, Cohen, & Beckwith, 1997).

After the age of 3 months, through the maturation of collicular–basal ganglia functions and the development of the posterior attention systems (Posner, Petersen, Fox, & Raichle, 1988), there is a developmental shift to sensory-specific attention (Karmel & Gardner, 2005; Geva et al., 1999a, 1999b; Johnson, Posner, & Rothbart, 1991). During this period, through mediation of norepinephrine and dopamine, modulation of attention affords the adaptive coordination of vigilance and distress during information processing (Eckerman, Oehler, Hannan, & Molitor, 1995). The second relevant milestone is the connectivity to the limbic system. Tucker and colleagues (2005) proposed that two midbrain structures, the hypothalamus and thalamus, are pivotal in organizing internal and external influences to ensure homeostasis of complex vertebrates. The hypothalamus is central in securing visceral regulation of internal states, such as hunger, thirst, temperature, and pain, and the thalamus at the top of the brainstem mediates the sensory and motor interfaces via projections to the telecephalon, trafficking limbic input as to the potential value of external inputs.

The transition to self-regulatory behaviors during the second year of life often draws upon higher control systems, reflecting the integration of the anterior cingulate gyrus that is implicated in the coordination of distress and attention. The cingulate is an integral component of the limbic system. The functional connectivity to prefrontal loci marks the final steps of the development of this system by exerting inhibitory control (Diamond, 1990). Thus, we propose that even transitory dysfunction of brainstem structures at the newborn period may disrupt the maturation of the entire system that supports behavior and emotion regulation.

Although links have been found between physiological regulation and outcomes in preterm infants, no information is typically provided on the specific neuro-pathogenesis leading to emotion dysregulation. Several researchers have proposed mechanisms that may mediate the effects of prematurity on emotion regulation. Anand and Scalzo (2000) described two pathways by which prematurity disrupts behavior organization. Stimulus overload related to early maternal separation leads to apoptosis (programmed cell-death) in multiple areas of the immature brain. Additionally, exposure of the immature CNS to pain causes excessive excitatory amino acid activation resulting in excitotoxic damage to developing neurons. Neurologically, these conditions may lead to changes in prelimbic prefrontal areas, causing increased excitation and hyper-reactivity (Risterucci, Terramorsi, Nieoullon, & Amalric, 2003). Behaviorally, both conditions are expressed in disturbed reactivity, difficulties in

sustained attention, and inability to self-regulate (Chudasama et al., 2003).

A conceptual model for the effects of neonatal brainstem dysfunction on behavior and emotion regulation: risk and protective factors

The proposed model describes the behavioral regulatory manifestations of neurobiological maturational changes that emerge as a function of time, exposure to stimulation, and neural integrity. The model proposes three levels of direct and mediated hypotheses according to three hierarchical and nested levels, originating in the assessment of brainstem functions. The first level includes physiological regulation of cyclic processes and sensory integration processes; the second level relates to further integration of three aspects of emotion and attention regulation; and the final level includes an integration of higher-level complex behavioral outputs. Direct relations address links between components at each level and the level directly above it. Long-term, potentially mediated relations refer to links between each level with an outcome measure one or two levels above, which may be either direct or mediated by factors at the same or at lower levels. For instance, relations between brainstem dysfunction and both arousal modulation and stress reactivity (Level 2) are expected. Such relations may be mediated by (a) physiological regulation of cyclic processes and sensory integration (Level 1), (b) mother–infant co-regulation (Level 2), or (c) both.

Evidence for the direct and mediated hypotheses of the model

Evidence regarding the hypothesized direct and mediated links is presented in the model along two interdependent paths: 1) linking brainstem dysfunction with cognitive processing and inhibitory control, and 2) linking brainstem dysfunction with socio-emotional self-regulation.

1: *Effects of brainstem dysfunction on cognitive processing and inhibitory control.* Two interdependent paths are proposed to account for the proposed brainstem effects on cognitive processing and inhibitory control (Figure 2).One path is through state regulation and the other path passes through attention regulation. Examples of these are presented in turn.

(a) *Physiological regulation of arousal: sleep–wake cyclicity and cardiac tone.* Abundant knowledge, using animal models, human adults, and infant studies, confirms that the monitoring of physiological regulatory status is located in multiple vital locales in the brainstem. Those include the biological clocks and the cyclic autonomic changes regarding state, satiety, temperature, and heart rate (Porges, 1997; Geva & Feldman, in press). Selected groups of premature infants exhibit disturbed rhythms of activity and rest (Feldman, Weller, Sirota, & Eidelman, 2002), indicating relations between compromised CNS and the development of physiological rhythms.

Porges' (1997) polyvagal evolutionary theory proposes that the nucleus ambiguus moderates the control of respiratory sinus arrhythmia, a function unique to the mammalian brainstem organization and related to processes of attention, emotion, and communication in humans. The polyvagal theory is consistent with the developmental vertical-integrative model in proposing brainstem involvement in higher cognitive and social-emotional processes. Cardiac vagal-tone, a measure of respiratory sinus arrhythmia, provides an index of attention regulation in newborns (Arditi, Feldman, & Eidelman, 2006), orientation in neonates (Feldman, 2006), and information processing during the first months of life (Bornstein & Suess, 2000). Similarly, sustained heart rate lowering during visual fixation marks voluntary, sustained attention in infants (Richards & Cronise, 2000). Respiratory sinus arrhythmia is related to an increase in vagal firing during sustained attention and to its inhibition at attention termination. Heart rate variability in the newborn period was found to predict cognitive development at 3 years in premature infants (Huffman et al., 1998). Cardiac vagal-tone in preterm neonates was found to determine the trajectories of cognitive and social emotional development from birth to 5 years of age (Feldman & Eidelman, in press) and sleep–wake cyclicity predicted sustained exploration at 6 months in premature infants (Feldman et al., 2002). These data point to bi-directional relations between the cyclicity of arousal, attention orientation, and circadian rhythmicity, functions mediated by brainstem-related systems, which contribute to information processing and cognitive competencies among premature infants.

(b) *Arousal-modulated attention (AMA).* Evidence points to the relations between physiological status and attention. For instance, when less aroused and

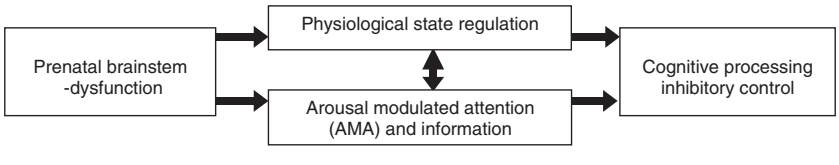

Figure 2

following feeding, full-term neonates look at more stimulating and novel events, and when more aroused, such as during the period before feeding, they look at less stimulating and familiar events. Such modulation is significantly altered in high-risk infants (Gardner et al., 2003). The greater the CNS insult, a lower change in attention toward higher stimulation or novelty would occur during states of lower arousal. This pattern of neonatal arousal-modulated attention differentiates normal neonates from infants with compromised brainstem functioning (CBSF; Karmel et al., 1996). Furthermore, feeding-based arousal also modulates visual recognition memory in early infancy, such that infants are able to prefer novel stimuli when less aroused (Geva et al., 1999a, 1999b). At 3 and 6 months of age, the cyclical pattern of arousal during habituation has been shown to determine the efficiency of infants' information processing in terms of processing speed and recognition memory (Feldman & Mayes, 1999).

The development of higher levels of output regulation requires inhibitory control capacities that would allow for stopping, reflecting, and considering options prior to the execution of output. Deficits in inhibitory control and executive attention may be reflected in the child's difficulties in making mental or behavioral shifts, which result in perseverative, impulsive, or distractible behavior (Diamond, 1990; Feldman, Gardner, Karmel, & Freedland, 1999a). These phenomena accord well with Rueda, Posner, and Rothbart's (2005) conceptualization on the contribution of attention networks to the development of self-regulation and executive control. Hence, it appears that over the long term CBSF may affect the development of regulatory capacities by interfering with the development of inhibitory control and cognitive self-regulation.

2. *Effects of brainstem dysfunction on social-emotional self-regulation.* Models of development and psychopathology emphasize the cumulative and interactive effects of risk factors on child outcomes and the ongoing interaction between the child and the social environment in shaping development (Cicchetti & Cohen, 1995) (Figure 3). Specific risk factors may be more disruptive to the infant's social environment, and certain environments may be more or less ready to respond to the excessive needs of a high-risk infant. In addition to the effects of risk, resilience components in the child and the family interact with risk variables in shaping developmental trajectories (Sameroff & Rosenblum, 2006). A child with more regulated dispositions, for example, may elicit more positive parenting, leading to improved emotion regulation and self-regulatory capacities even among infants at greater biological risk.

A multi-level model of self-regulation in children with CBSF reflects the interaction of risk (e.g., brainstem dysfunction) and resiliency (e.g., mother–child co-regulation and synchrony) factors. Similarly, the early development of brainstem structures is moderated by social interactions. Neonatal development of the vertical-integrative system is thus hypothesized to be mediated by the nature of early social interactions. Early maturing arousal systems are shaped by the rapid maturation of the reticular activating system in the brainstem and the effects of environmental stimulation and social interactions (Schore, 1997) and mother–infant contact and synchrony shape the infant's emerging regulatory skills (Feldman, 2007a). Thus, a developmental model should accommodate both brain programming maturational processes and openness to environmental stimulation to account for the development of behavioral and emotional regulation.

Two interdependent paths are proposed in the model to account for the effects of brainstem systems on socio-emotional self-regulatory skills. The first path passes through the development of emotion regulation and stress reactivity path and the second passes through the mother–infant co-regulation and synchrony. As to the first path, brainstem-related mechanisms were shown to be activated in preterm infants during emotional arousal. Cardiac vagal-tone has been shown to predict infants' response to intrusive environmental stimulation (Huffman et al., 1998; Bazhenova, Plonskaia, & Porges, 2001; Feldman, 2006). Relationships between satiety and social behavior were also found. This relationship was shown in lambs, which exhibit differences in preferential relationship with the mother as a function of nutritional and non-nutritional signals originating from the gastrointestinal region, via mediation of cholecystokinin (CCK; Weller & Feldman, 2003). This body of research highlights the major role of post-ingestive mechanisms played by the gut–brain axis in the development of filial bonding (Val-Laillet, Simon, & Nowak, 2004).

As to the second path, which focuses on the mother's role in the development of self-regulation, Hofer's (1995) model on 'hidden regulators' under-

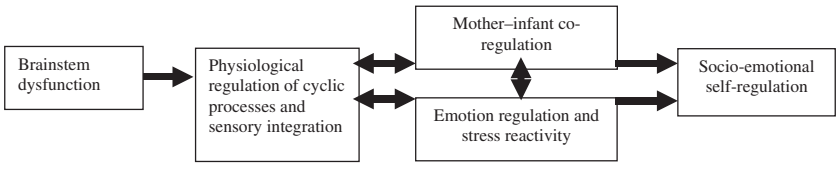

Figure 3

scores the role of maternal proximity and contact in the post-birth period to the infant's physiological regulation. Maternal milk, touch, smell, body heat, and biological rhythms provide a set of bio-behavioral regulators to the infant's autonomic, thermoregulation, feeding, and stress-management systems, most of which are mediated by the brainstem. Hence, maternal–infant contact provides the basis for the development of physiological and emotional regulatory processes (Ferber, Laudon, Kuint, Weller, & Zisapel, 2002; Feldman, 2004). Early contact improves the infant's emotion regulation, stress reactivity, and social and cognitive development (Feldman et al., 2002), pointing to the role of contact, as moderated by brainstem systems, in the development of appropriate mechanisms of stress and emotional coping.

The developmental sequence of social-emotional self-regulation is bi-directional. Maternal touch affects the secretion of brainstem-related biochemical substances that mediate homeostasis, comfort, and arousal (Poeggel et al., 1999). Studies showed that there is a relationship between secretion of gut hormones (CCK) and touch effects in pups (Weller & Feldman, 2003). Scheduled maternal touch, applied to term infants in the early postnatal period, organized the infant's activity–rest cycle (8 weeks) and regulated melatonin rhythms during the nocturnal period (12 weeks; Ferber et al., 2002). These results imply that maternal touch in the perinatal period serve as a zeitgeber-moderator to enhance brainstem-related coordination of the developing circadian system with environmental cues. Together, these findings point to the interrelationships between physiological regulation, stress reactivity, and maternal–infant co-regulation (Feldman, 2007a, 2007b). It may also suggest that maternal–infant co-regulation, in the form of bodily contact or affective synchrony, may facilitate the development of self-regulation even among infants born with brainstem dysfunctions.

Socio-emotional self-regulation capacities of children with CBSF are likely to be compromised. According Kopp (1982), self-regulation is built on the maturation of inhibitory functions as well as on the mutuality between mother and infant. Kochanska, Murray, and Coy (1997) showed that toddlers' inhibitory control and mother–child emotional responsiveness independently predicted socialized compliance, and mother–infant affect synchrony at 3 and 9 months was found to predict the development of self-regulation at 2 years (Feldman, Greenbaum, & Yirmiya, 1999b). Self-regulation, socialization, and moral internalization were found to be predicted by physiological self-regulation, inhibitory control, and mother–infant affect synchrony (Feldman, 2007a). In turn, a longitudinal follow-up from infancy to adolescence showed that affect synchrony at 3 months has a direct impact on the development of the child's moral orientation and empathy at 13 years (Feldman, 2007b). As such, brainstem dysfunction in preterm infants or in affected neonates, with its ensuing regulatory deficits, is thus likely to have a negative impact on the development of social-emotional regulatory skills.

Overall the conceptual model highlights potential longitudinal links between brainstem functions and the development of regulatory capacities across early childhood in several areas of development, including physiological systems, attention, stress, and parent–infant synchrony. There is sufficient data to support the hypotheses both within each level of the model and between lower and higher levels. Previous studies support the proposed links between disruption to brainstem system and difficulties at the level of physiological regulation, between physiological homeostatic systems and the development of emotion regulation, attention modulation, and stress reactivity, and between those and the development of higher-order cognitive and social processes.

Based on the aforementioned studies, direct relations are also proposed between non-adjacent levels of the model. For instance, the model proposes links between brainstem-mediated physiological functions, such as cardiac vagal-tone with higher-order cognitive and social self-regulatory outcomes, which may be either direct or mediated by attention modulation and stress management. Finally, the model presents hypothesized relations that call for further research, particularly between brainstem functioning and higher-order prefrontally-mediated functions, such as socio-emotional regulation, or between brainstem dysfunction and disorders in higher cortically-mediated skills, such as observed in attention deficit and hyperactivity disorder or conduct disorder.

Expected significance of the vertical integrated model

The vertical-integrative model offers several unique windows into important current issues, such as prenatal and perinatal trauma and recovery, the neurological basis of emotions and self-regulation, and the role of the environment in shaping developmental outcomes of specific prenatal and perinatal pathological processes which implicate brainstem systems. Several points are highlighted by the model. First, the model incorporates multidimensional regulatory expressions of the CBSF phenomenon: *biochemical* (e.g., melatonin, cortisol), *autonomic* (vagal-tone; sleep; feeding), *attentional-cognitive* (e.g., arousal-modulated attention, inhibitory control); *emotional reactivity to stress*; and *co-regulation of emotional responsivity. These interdependent expressions are proposed to set the foundation for the development of higher-order complex cognitive and emotional processes*. Second, the model allows for

better understanding of the relations between domains of performance (e.g., attentional versus socio-emotional) and proposes links between these domains of functioning. Third, the model points to an important yet understudied area of research – brainstem functioning. It may drive further research on the specific paths leading from compromised brainstem functioning to the development of cognitive effortful control and socio-emotional regulation of behavior, and such future work will shape and specify the proposed preliminary model. Fourth, the model suggests potential mechanisms for the development of self-regulation in the emotional and behavioral domains that may be applied to *developmental theory* in general. Fifth, the model proposes *pathways of recovery* from neonatal brainstem – related pathogenic processes in a developing system. Finally, the model implies that perinatal diagnosis of CBSF may afford specific guidelines to neonatologists, clinicians, and parents rearing children who are at risk for behavioral and emotional dysregulation by providing more specific information for diagnosis, intervention, and social policies.

Implications of the vertical-integrative model for early diagnosis of infants born prematurely

The aforementioned developmental progression of the vertical-integrative model highlights the importance of assessing dysfunctions related to lower levels of CNS functioning, particularly of brainstem dysfunctions, already at the NICU. Disruptions to the development of these lower-level systems can serve as important indicators of risk for the emergence of self-regulatory capacities.

An ABR evaluation may be a particularly valuable diagnostic tool for premature infants during the neonatal phase, since it has specific features that are identified as dependent on maturation (Karmel et al., 1988). ABR recordings in preterm infants first appear at 26 weeks of gestation, around the age of extra-uterine viability. The ABR function then undergoes detectable maturational changes until 34 weeks' gestational age and thus overlaps the period of NICU care for most preterm neonates. During this period, ABR functions are highly sensitive to acute complications, and these are observed by systematic changes in the latency, amplitude, or threshold of the ABRs. Using supra-threshold intensities of 60 dB hearing level or more, it is evocable in all newborn infants with at least some minimal hearing capacities (Karmel et al., 1988; Jiang et al., 2004).

In view of the vertical-integrated framework model, evaluation of brainstem functioning in the final weeks of pregnancy or in premature infants is highly informative. It is also feasible. Structural integrity of the CNS is routinely assessed in NICUs with cranial ultra-sound (US) and/or MRI within the first days of life (Volpe, 1995; Woodward, Anderson, Austin, Howard, & Inder (2006). Functional integrity of the CNS is sometimes evaluated in the same period by ABR recordings using portable evoked potential equipment (Karmel et al., 1988; Jiang et al., 2007).

Advances in medical care have resulted in a marked decrease in severe intracranial hemorrhage. However, there is no indication of any decrease in the suspected involvement of brainstem and other subcortical regions (Volpe, 1995). These regions are difficult to visualize by ultrasound or by MRI (Volpe, 1995; Fraser et al., 2007), but are easily studied functionally by ABRs (Jiang et al., 2007; Wilkinson et al., 2007). Although providing different forms of information, agreement between cranial ultrasound and evoked potential procedures is high, between 78% and 86% (Karmel et al., 1988). The disagreements probably reflect foremost substantive differences in regional CNS injuries, their differential courses of recovery, or the distinction between structural and functional integrity of the CNS.

In view of the vertical-integrative framework, we suggest that early evaluations of brainstem and lower-level structures in infants born preterm and even in fetuses may be highly informative as a potential early marker of self-regulation deficits. Since vulnerabilities in ABR functions have been reported in preterm infants born between 30 and 34 weeks' gestation (Pasman, Rotteveel, de Graaf, Maassen, & Visco, 1996), infants born at these ages at low medical risk may still present compromised brainstem functioning. Such assessment is particularly important for infants born before the full maturation of brainstem functions (i.e., before 34 weeks' gestation). Detection of neonatal brainstem dysfunctions may help target infants who are at risk for self-regulation deficits and allow for specific early interventions that may improve the self-regulatory difficulties so commonly observed in premature infants across childhood and beyond.

Acknowledgements

Supported by the US-Israel Bi-National Science Foundation (# 2001-241).

Correspondence to

Ronny Geva, The Gonda Goldschmied Brain Research Center, Bar Ilan University, Ramat Gan, Israel 52900; Email: gevaro@mail.biu.ac.il

References

Abadie, V., Morisseau-Durand, M.P., Beyler, C., Manach, Y., & Couly, G. (2002). Brainstem dysfunc-

tion: A possible neuroembryological pathogenesis of isolated Pierre Robin sequence. *European Journal of Pediatrics*, *161*, 275–280.

Anand, K.J., & Scalzo, F.M. (2000). Can adverse neonatal experiences alter brain development and subsequent behavior? *Biology of the Neonate*, *77*, 69–82.

Arditi, H., Feldman, R., & Eidelman, A.I. (2006). Effects of human contact and vagal regulation on pain reactivity and visual attention in newborns. *Developmental Psychobiology*, *48*, 561–573.

Batterham, R.L., ffytche, D.H., Rosenthal, J.M., Zelaya, F.O., Barker, G.J., Withers, D.J., & Williams, S.C. (2007). PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature*, *450*, 106–109.

Bazhenova, O.V., Plonskaia, O., & Porges, W.S. (2001). Vagal reactivity and affective adjustment in infants during interaction challenges. *Child Development*, *72*, 1287–1604.

Bornstein, M.H., & Suess, P.E. (2000). Physiological self-regulation and information processing in infancy: Cardiac vagal tone and habituation. *Child Development*, *71*, 273–287.

Caldji, C., Francis, D., Sharma, S., Plotsky, P.M., & Meaney, M.J. (2000). The effects of early rearing environment on the development of GABA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology*, *22*, 219–229.

Chudasama, Y., Passetti, F., Rhodes, S.E., Lopian, D., Desai, A., & Robbins, T.W. (2003). Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: Differential effects on selectivity, impulsivity and compulsivity. *Behavioral Brain Research*, *30*, 105–119.

Cicchetti, D., & Cohen, D.J. (1995). *Developmental psychopathology*. New York: Wiley.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., & Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience*, *3*, 1049–1056.

Darnall, R.A., Ariagno, R.L., & Kinney, H.C. (2006). The late preterm infant and the control of breathing, sleep, and brainstem development: A review. *Clinics in Perinatology*, *33*, 883–914.

Dennis, T. (2006). Emotional self-regulation in preschoolers: The interplay of child approach reactivity, parenting, and control capacities. *Developmental Psychology*, *42*, 84–97.

Diamond, A. (1990). The development and neural bases of memory functions as indexed by the AB and delayed response tasks in human infants and infant monkeys. In A. Diamond (ed.), *The development and neural bases of higher cognitive functions. Annals of the New York Academy of Sciences. vol. 608*, pp. 267–317). New York: The New York Academy of Sciences.

Eckerman, C.O., Oehler, J.M., Hannan, T.E., & Molitor, A. (1995). The development prior to term age of very prematurely born newborns' responsiveness in en face exchanges. *Infant Behavior and Development*, *17*, 55–70.

Ellenbogen, M.A., Schwartzman, A.E., Stewart, J., & Walker, C.D. (2006). Automatic and effortful emotional information processing regulates different aspects of the stress response. *Psychoneuroendocrinology*, *31*, 373–387.

Feldman, R. (2004). Mother–infant skin-to-skin contact and the development of emotion regulation. In S.P. Shohov (Ed.), *Advances in psychology research* (*vol. 27*, pp. 113–131). Hauppauge, NY: Nova Science.

Feldman, R. (2006). From biological rhythms to social rhythms: Physiological precursors of mother–infant synchrony. *Developmental Psychology*, *42*, 175–188.

Feldman, R. (2007a). Parent–infant synchrony and the construction of shared timing; Physiological precursors, developmental outcomes, and risk conditions. *Journal of Child Psychology and Psychiatry*, *48*, 329–354.

Feldman, R. (2007b). Mother–infant synchrony and the development of moral orientation in childhood and adolescence: Direct and indirect mechanisms of developmental continuity. *American Journal of Orthopsychiatry*, *77*, 582–597.

Feldman, L.J., Gardner, J.M., Karmel, B.Z, & Freedland, R.L. (1999a). *Development of focused attention from 10 to 16 months in low- and high-risk infants*. Paper presented at ECDP meeting, Spetses, Greece, September.

Feldman, R., & Eidelman, A.I. (in press). Biological and environmental initial conditions shape the trajectories cognitive and social-emotional development across the first five years of life. *Developmental Science*.

Feldman, R., Greenbaum, C.W., & Yirmiya, N. (1999b). Mother–infant affect synchrony as an antecedent to the emergence of self-control. *Developmental Psychology*, *35*, 223–231.

Feldman, R., & Mayes, L.C. (1999). The rhythmic organization of infant attention during habituation is related to infants' information processing. *Infant Behavior and Development*, *22*, 37–49.

Feldman, R., Weller, A., Sirota, L., & Eidelman, A.I. (2002). Skin-to-skin contact (kangaroo care) promotes self-regulation in premature infants: Sleep–wake cyclicity, arousal modulation, and sustained exploration. *Developmental Psychology*, *38*, 194–207.

Ferber, S.G, Laudon, M., Kuint, J., Weller, A., & Zisapel, N. (2002). Massage therapy by mothers enhances the adjustment of circadian rhythms to the nocturnal period in full-term infants. *Journal of Developmental and Behavioral Pediatrics*, *23*, 410–415.

Fraser, M., Bennet, L., Helliwell, R., Wells, S., Williams, C., Gluckman, P., Gunn, A.J., & Inder, T. (2007). Regional specificity of magnetic resonance imaging and histopathology following cerebral ischemia in preterm fetal sheep. *Reproductive Science*, *14*, 182–191.

Galambos, R., Hicks, G., & Wilson, M.J. (1982). Hearing loss in graduates of a tertiary intensive care nursery. *Ear and Hearing*, *3*, 87–90.

Gardner, J.M., Karmel, B.Z., & Flory, M.J. (2003). Arousal modulation of neonatal visual attention: Implications for development. In S. Saroci (Ed.), *Perspectives on fundamental processes in intellectual functioning: Vol. 2. Visual information processing and*

individual differences. Stamford, CT: Ablex, JAI (Elsevier).

Gardner, J.M., & Karmel, B.Z. (1995). Development of arousal-modulated visual preferences in early infancy. *Developmental Psychology*, *31*, 473–482.

Geva, R. (1995). *Relationships between neonatal risk, cognitive development and inhibitory control at three years of age*. Unpublished doctoral dissertation. New York: City University of New York.

Geva, R., Eshel, R., Leitner, Y., Fattal-Valevski, A., & Harel, S. (2005). Prenatal diagnosis and management of intrauterine growth retardation (IUGR): A long-term prospective study on outcome and maternal coping. *Infant Mental Health Journal*, *26*, 481–495.

Geva, R., & Feldman, R. (in press). Circadian sleep–wake rhythms in preterm infants. In F. Columbus, (Ed), *Circadian rhythms and health research trends. Advances in psychology research*. Hauppauge, NY: NOVA Science Publishers.

Geva, R., Gardner, J.M., Karmel, B.Z., Feldman, I.J., & Freedland, R.L. (1999a). Inhibitory control of cocaine-exposed infants at 3 years. In L.S. Harris (ed.), *Problems of drug dependence 1998 (NIDA Research Monograph No. 179, 98)*. Washington, DC: Department of Health and Human Services.

Geva, R., Gardner, J.M., & Karmel, B.Z. (1999b). Feeding-based arousal effects on visual recognition memory in early infancy. *Developmental Psychology*, *35*, 640–650.

Geva, R., Gardner, J.M., & Karmel, B.Z. (June, 2004). *Non-competitive information load effect on a rapid sequential automated naming task (RSANT)*. A poster presented at Conference on Human Development, Washington, DC.

Gunnar, M.R., & Quevedo, K.M. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, *58*, 145–173.

Hack, M., Taylor, H.G., Klein, N., Eiben, R., Schatschneider, C., & Mercuri-Minich, N. (1994). School-age outcomes in children with birth weights under 750g. *New England Journal of Medicine*, *331*, 753–759.

Hofer, M.A. (1995). Hidden regulators: Implication for a new understanding of attachment, separation, and loss. In S. Golberg, R. Muir, & J. Kerr (Eds.), *Attachment theory: Social, developmental, and clinical perspectives* (pp. 203–230). Hillsdale, NJ: Analytic Press.

Huffman, L.C., Bryan, Y.E., del Carmen, R., Pedersen, F.A., Doussard-Roosevelt, J.A., & Porges, S.W. (1998). Infant temperament and cardiac vagal tone: Assessments at twelve weeks of age. *Child Development*, *69*, 624–635.

Hunt, C.E. (2006). Ontogeny of autonomic regulation in late preterm infants born at 34–37 weeks post-menstrual age. *Seminars in Perinatology*, *30*, 73–76.

Jentsch, J.D., Roth, H.R., & Taylor, J.R. (2000). Role for dopamine in the behavioral functions of the prefrontal corticostriatal system: Implications For mental disorders and psychotropic drug addiction. *Progress in Brain Research*, *126*, 433–453.

Jiang, Z., Brosi, D.M., & Wilkinson, A.R. (2006). Brainstem auditory function in very preterm infants with chronic lung disease: Delayed neural conduction. *Clinical Neurophysiology*, *117*, 1551–1559.

Jiang, Z.D., Xiu, X., Brosi, D.M., Shao, X.M., & Wilkinson, A.R. (2007). Sub-optimal function of the auditory brainstem in term infants with transient low Apgar scores. *Clinical Neurophysiology*, *118*, 1088–1096.

Jiang, Z.D., Yin, R., Shao, X.M., & Wilkinson, A.R. (2004). Brain-stem auditory impairment during the neonatal period in term infants after asphyxia: Dynamic changes in brain-stem auditory evoked response to clicks of different rates. *Clinical Neurophysiology*, *115*, 1605–1615.

Johnson, M.H., Posner, M.I., & Rothbart, M.K. (1991). Components of visual orienting in early infancy: Contingency learning, anticipatory looking, and disengaging. *Journal of Cognitive Neuroscience*, *3*, 335–344.

Jongmans, M., Mercuri, E., DeVries, L., Dubowitz, L., & Henderson, S.E. (1997). Minor neurological signs and perceptual-motor difficulties in prematurely born children. *Archives of disease in childhood*, *76*, F9–F14.

Karlsson, K.A., Gall, A.J., Mohns, E.J., Seelke, A.M., & Blumberg, M.S. (2005). The neural substrates of infant sleep in rats. *PLoS Biology*, *3*, e143.

Karmel, B.Z., & Gardner, J.M. (2005). Neurobehavioral assessment in the neonatal period – the impact of Ferenc Katona. *Ideggyogy Sz.*, *58*, 315–323.

Karmel, B.Z., Gardner, J.M., & Freedland, R.L. (1996). Arousal-modulated attention at four months as a function of intrauterine cocaine exposure and central nervous system injury. *Journal of Pediatric Psychology*, *21*, 821–832.

Karmel, B.Z., Gardner, J.M., Zappulla, R.A., Magnano, C.L., & Brown, E.G. (1988). Brainstem auditory evoked responses as indicators of early brain insult. *Electroencephalography and Clinical Neurophysiology*, *71*, 429–442.

Kochanska, G., Murray, K., & Coy, K.C. (1997). Inhibitory control as a contributor to conscience in childhood: From toddler to early school age. *Child Development*, *68*, 263–277.

Kopp, C.B. (1982). Antecedents of self-regulation: A developmental perspective. *Developmental Psychology*, *18*, 199–214.

Krumholz, A., Felix, J.K., Goldstein, P.J., & McKenzie, E. (1985). Maturation of the brain stem auditory evoked potential in premature infants. *Electroencephalography and Clinical Neurophysiology*, *62*, 124–134.

Merker, B. (2007). Consciousness without a cerebral cortex: A challenge for neuroscience and medicine. *Behavioral and Brain Sciences*, *30*, 63–81.

Moore, J.K., Perazzo, L.M., & Braun, A. (1995). Time course of axonal myelination in the human brainstem auditory pathway. *Hearing Research*, *87*, 21–31.

Morilak, D.A., Barrera, G., Echevarria, D.J., Garcia, A.S., Hernandez, A., Ma, S., et al. (2005). Role of brain norepinephrine in the behavioral response to stress. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*, 1214–1224.

Murray, A.D. (1988). Newborn auditory brainstem evoked responses (ABRs): Longitudinal correlates in the first year. *Child Development*, *59*, 1542–1554.

Panksepp, J. (2005). Affective consciousness: Core emotional feelings in animals and human. *Consciousness and Cognition*, *14*, 30–80.

Pasman, J.W., Rotteveel, J.J, de Graaf, R., Maassen, B., & Visco, Y.M. (1996). The effects of early and late preterm birth on brainstem and middle-latency auditory evoked responses in children with normal neurodevelopment. *Journal of Clinical Neurophysiology*, *13*, 234–241.

Poeggel, G., Lange, E., Hase, C., Metzger, M., Gulyaeva, N., & Braun, K. (1999). Maternal separation and early social deprivation in Octodon degua: Quantitative changes of nicotinamide adenine dinucleotide phosphate-diaphorase-reactive neurons in the prefrontal cortex and nucleus accumbens. *Neuroscience*, *94*, 497–504.

Porges, S.W. (1992). Vagal tone: A physiologic marker of stress vulnerability. *Pediatrics*, *90*, 498–504.

Porges, S.W. (1997). Emotion: An evolutionary by-product of the neural regulation of the autonomic nervous system. *Annals of the New York Academy of Sciences*, *807*, 62–77.

Posner, M.I., Petersen, S.E., Fox, P.T., & Raichle, M.E. (1988). Localization of cognitive operations in the human brain. *Science*, *217*, 1627–1631.

Posner, M.I., Rothbart, M.K., & Sheese, B.E. (2007). Attention genes. *Developmental Science*, *10*, 24–29.

Richards, J.E., & Cronise, K. (2000). Extended visual fixation in the early preschool years: Look duration, heart rate changes, and attentional inertia. *Child Development*, *71*, 602–620.

Risterucci, C., Terramorsi, D., Nieoullon, A., & Amalric, M. (2003). Excitotoxic lesions of the prelimbic–infralimbic areas of the rodent prefrontal cortex disrupt motor preparatory processes. *European Journal of Neuroscience*, *17*, 1498–1508.

Roig, Q.M., Gratacos, M., Vazquez, E., Del Toro, M., Foguet, A., Ferrer, I., & Macaya, A. (2003). Brainstem dysgenesis: Report of five patients with congenital hypotonia, multiple cranial nerve involvement, and ocular motor apraxia. *Developmental Medicine and Child Neurology*, *45*, 489–493.

Rothbart, M.K., & Rueda, M.R. (2005). The development of effortful control. In U. Mayr, E. Awh, & S.W. Keele (Eds.), *Developing individuality in the human brain: A tribute to Michael I. Posner* (pp. 167–188). Washington, DC: American Psychological Association.

Rothbart, M.K., Sheese, B.E., & Posner, M.I. (2007). Executive attention and effortful control: Linking temperament, brain networks, and genes. *Child Development Perspectives*, *1*, 2–7.

Rueda, M.R., Posner, M.I., & Rothbart, M.K. (2005). The development of executive attention: Contributions to the emergence of self-regulation. *Developmental Neuropsychology*, *28*, 573–594.

Salamy, A., & Eldredge, L. (1994). Risk for ABR abnormalities in the nursery. *Electroencephalography and Clinical Neurophysiology*, *92*, 392–395.

Sameroff, A.J., & Rosenblum, K.L. (2006). Psychosocial constraints on the development of resilience. *Annals of New York Academy of Sciences*, *1094*, 116–124.

Schore, A.N. (1997). Early organization of the nonlinear right brain and development of a predisposition to psychiatric disorders. *Development and Psychopathology*, *9*, 595–631.

Sigman, M., Cohen, S.E., & Beckwith, L. (1997). Why does infant attention predict adolescent intelligence? *Infant Behavior and Development*, *20*, 133–140.

Skranes, J., Vangberg, T.R., Kulseng, S., Indredavik, M.S., Evensen, K.A., Martinussen, M., et al. (2007). Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain*, *130*, 654–666.

Tucker, D.M., Luu, P., & Derryberry, D. (2005). Love hurts: The evolution of empathic concern through the encephalization of nociceptive capacity. *Development and Psychopathology*, *17*, 699–713.

Valkama, A.M., Tolonen, E.U., Kerttul, L.I., Paakko, E.L., Vainionpaa, L.K., & Koivist, M.E. (2001). Brainstem size and function at term age in relation to later neurosensory disability in high-risk, preterm infants. *Acta Paediatrica*, *90*, 909–915.

Val-Laillet, D., Simon, M., & Nowak, R. (2004). Full belly and colostrum: Two major determinants of filial love. *Developmental Psychobiology*, *45*, 163–173.

Volpe, J.J. (1995). Brain injury in the premature infant – current concepts. *Preventative Medicine*, *23*, 638–645.

Weller, A., & Feldman, R. (2003). Emotion regulation and touch in infants: The role of cholecystokinin and opioids. *Peptides*, *24*, 779–788.

Wilkinson, A.R., Brosi, D.M., & Jiang, Z.D (2007). Functional impairment of the brainstem in infants with bronchopulmonary dysplasia. *Pediatrics*, *120*, 362–371.

Woodward, L.J., Anderson, P.J., Austin, N.C., Howard, K., & Inder, T.E. (2006). Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *New England Journal of Medcine*, *355*, 685–694.

Zeskind, P.S., Goff, D.M., & Marshall, T.R. (1991). Rhythmic organization of neonatal heart rate and its relation to atypical fetal growth. *Developmental Psychobiology*, *24*, 413–429.

Manuscript accepted 25 February 2008