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The Biological Embedding of Neonatal Stress Exposure: A Conceptual Model Describing the Mechanisms of Stress-Induced Neurodevelopmental Impairment in Preterm Infants

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Abstract

The biological embedding of early life stress exposure may result in life-long neurodevelopmental impairment in preterm infants. Infants hospitalized in the neonatal intensive care unit are exposed to significant experiential, environmental, and physiologic stressors over the course of their extended hospitalization. Stress exposure during the sensitive period of brain development may alter biological processes, including functioning of the immune system, the autonomic nervous system, and the hypothalamic-pituitary-adrenal axis as well as gene expression. These alterations may subsequently affect brain structure and function. Changes to these processes may mediate the relationship between neonatal stress exposure and neurodevelopment in preterm infants and represent potential therapeutic targets to improve long-term outcomes. The purpose of this paper is to introduce a conceptual model, based on published research, that describes the mechanisms mediating stress exposure and neurodevelopment impairment in preterm infants and to provide the theoretical foundation on which to base future descriptive research, intervention studies, and clinical care.

Keywords

preterm infant; stress; neurodevelopment; theory

Preterm birth is a significant public health concern, accounting for nearly 10% of births in the United States in 2015 (Martin, Hamilton, & Osterman, 2016). Advances in medical technology have increased the rate of survival for many preterm infants such that the majority of infants born after 23 weeks post-menstrual age survive (Manuck et al., 2016); however, the long-term neurodevelopmental outcomes of these infants remains a concern (Luu, Rehman Mian, & Nuyt, 2017). Billions of dollars are spent annually in the United

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States for prematurity-related special education and early intervention services (Institute of Medicine [IOM], 2007).

Although 70-88% of very preterm infants will receive early intervention services to optimize their development (Clements, Barfield, Ayadi, & Wilber, 2007), many still suffer significant neurodevelopment deficits. Preterm birth accounts for over 50% of population level cases of cerebral palsy (CP) and over 10% of autism spectrum disorders and intellectual disabilities (Schieve et al., 2016). As many as 50% of very low birthweight infants (i.e. infants born at less than 1500 grams) are diagnosed with neurodevelopmental impairments, including CP, intellectual disabilities, and psychopathologies (e.g. emotional problems, behavioral problems, anxiety disorders) by the time they have reached adolescence (Yang, Chen, Yen, & Chen, 2015).

In this paper, we define neurodevelopment broadly, as the neonate's capacity to interact in a reciprocal fashion with the environment by responding to environmental stimuli while maintaining physiologic stability (Bell, Lucas, & White-Traut, 2008). The infant's range of responses to environmental stimuli is developmentally determined and changes in a hierarchical manner over time (Bell et al., 2008) with responses becoming increasingly complex and varied as the infant acquires skills for state and physiologic regulation. Thus, neurodevelopment encompasses the infant's complete repertoire of cognitive, motor, language, sensory, and socio-emotional capacities. Compared to their term-born counterparts, preterm infants suffer more impairments in sensory development (Cabral, da Silva, Martinez, & Tudella, 2016), behavioral functioning (Cassiano, Gaspardo, & Linhares, 2016), motor functioning (Charkaluk, Truffert, Fily, Ancel, & Pierrat, 2010), and cognition (Ionio et al., 2016; Kallankari, Kaukola, Olsen, Ojaniemi, & Hallman, 2015). Many impairments, including deficits in executive functioning and academic performance and mental health concerns persist into late adolescence and early adulthood (Gough et al., 2015; Hack et al., 2004). Adults who were born very preterm are more likely than their term-born counterparts to experience nonaffective psychosis, depression, and bipolar disorder, which affect quality of life and productivity (Nosarti et al., 2012).

The causes of neurodevelopmental impairment in preterm infants are multifactorial and include hypoxemia (Poets et al., 2015), critical illness (Cassiano et al., 2016), and perinatal insults (Kallankari et al., 2015; Koc et al., 2016). In addition to these important factors, stress exposure is a critical determinant of neurodevelopmental outcomes beyond that predicted by other factors. Preterm infants admitted to the NICU are exposed to significant environmental, experiential, and physiologic stressors including medical procedures, nursing care, medical comorbidities, and pain (Lyngstad, Tandberg, Storm, Ekeberg, & Moen, 2014; Newnham, Inder, & Milgrom, 2009). Researchers have linked pain-related stress exposure in the NICU to long-term alterations in the stress response and impaired neurodevelopment (Grunau et al., 2013; Ranger et al., 2013; Valeri, Holsti, & Linhares, 2015). In a prospective, longitudinal study of preterm infants, those with greater neonatal stress exposure, operationalized as skin-breaking procedures, had poorer motor and cognitive functioning at 8 and 18 months corrected age than those with fewer skin-breaking procedures, controlling for neonatal illness severity (Grunau et al., 2009).

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Nurses occupy a unique position to test and implement innovative interventions to reduce stress exposure or its effects. Interventions to support infant development and reduce stress exposure, such as the Newborn Individualized Developmental Care and Assessment Program (Als & Gilkerson, 1997) and other similar programs, are associated with some improvement in preterm infant neurodevelopment (Burke, 2018; Peters et al., 2009). However, sustained, long-term effects of developmental interventions in the NICU and early intervention programs post-discharge have been difficult to demonstrate (Burke, 2018; Ohlsson & Jacobs, 2013; Spittle, Orton, Anderson, Boyd, & Doyle, 2015), and, thus, necessitate the development of novel interventions. The development of a testable model to identify mediators between stress exposure and neurodevelopment is a critical step in developing targeted interventions to improve long-term outcomes.

The purpose of this paper is to present a mechanistic conceptual model, the Neonatal Stress Embedding (NSE) model, which describes the biological embedding of neonatal stress exposure in the NICU and its effects on short and long-term neurodevelopment (Figure 1). Biological embedding is the process by which early life stress exposure during critical or sensitive periods of development affects long-term health outcomes through permanent changes to biological processes (Nist, 2017). Critical or sensitive periods are those during which rapid brain growth is occurring, making the brain vulnerable to environmental insults (Buschdorf & Meaney, 2015). The changes to biological processes may occur through the re-programming of the functional parameters of biological systems or through heritable epigenetic markings (Buschdorf & Meaney, 2015). In preterm infants, re-programming of the immune system, the autonomic nervous system, and the hypothalamic-pituitary-adrenal (HPA) axis, as well as changes in gene expression, may account for the biological embedding of stress exposure during NICU hospitalization.

We are aware of only one other model that describes the effect of neonatal stress exposure on preterm infant outcomes (Moore, Berger, & Wilson, 2014). The model by Moore et al. (2014) explains the effect of neonatal stress exposure using allostatic load as the central concept. We argue that a model describing the *biological embedding* of neonatal stress exposure more fully captures the effects of stress exposure on the preterm infant's developing and immature systems and is more consistent with literature on the developmental origins of health and illness (Howland, Sandman, & Glynn, 2017; Kubota, Miyake, Hariya, & Mochizuki, 2015). The NSE model is an alternative, and potentially complementary, conceptual model that may provide a more comprehensive explanation of the effect of early stress exposure in preterm infants.

In this paper, we provide a brief overview of brain development in the preterm infant, highlighting the vulnerability of the developing brain to stress exposure, and providing the context for the NSE model. Next, we present the central concepts of the model and provide empirical support for these concepts and their relationships. Finally, we discuss the research and practice implications for the NSE model.

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Vulnerability of the Developing Brain to Stress Exposure

Preterm Infant Brain Development

Significant brain development occurs during the last half of pregnancy, which is characterized by neural migration, particularly of the gamma aminobutyric acid inhibitory neurons; axonal and dendritic lengthening; synaptogenesis; selective apoptosis; and glial proliferation (Ortinau & Neil, 2015). These processes result in the final organization of the cerebral cortex. In addition, myelination, which is mediated by oligodendrocyte maturation, begins in the second trimester and continues through the postnatal and early childhood periods. Though a comprehensive examination of prenatal brain development is outside the scope of this paper, we refer readers to an excellent review by Ortinau and Neil (2015).

In preterm infants, these developmental processes must occur outside of the protective intra-uterine environment and in an intensive care unit, where they are vulnerable to environmental insults including stress exposure. Compared to term-born infants, neuronal connectivity in the basal ganglia and frontal regions of the brain are significantly altered in preterm infants without overt brain injury at term-equivalent age (Ball et al., 2016). Alterations in the brain's connectome following periventricular hemorrhage or ventricular dilation in preterm infants is associated with cognitive deficits in adulthood (Karolis et al., 2016). Stress exposure in the NICU is associated with decreased regional brain volumes and altered connectivity among preterm infants at term-equivalent age (Smith et al., 2011). While programmed cell death, or apoptosis, is a normal part of brain development, the repeated activation of stress pathways in the developing brain may result in aberrant apoptotic signaling, resulting in disruptions to neuronal connections and, ultimately, abnormal growth and organization of the cerebral cortex (Anand & Scalzo, 2000). Finally, oligodendrocytes, which undergo maturation during the second half of pregnancy, are especially vulnerable to inflammatory and ischemic insults, and damage to these cells contributes to white matter injury in preterm infants (Volpe, Kinney, Jensen, & Rosenberg, 2011). In summary, the human brain undergoes dramatic development and maturation during the second and third trimesters of gestation, making the preterm infant brain particularly susceptible to environmental insults and vulnerable to aberrant programming.

Neonatal Stress Exposure

Early life stress exposure during critical periods influences brain development and long-term neurodevelopmental outcomes, affecting brain structure and behavior, motor function, and stress reactivity (Valeri et al., 2015). Researchers have shown that extended NICU hospitalizations are associated with poorer outcomes on motor and cognitive developmental tests (Subedi, DeBoer, & Scharf, 2016). The relationship between stress exposure and neurodevelopment may be mediated by changes to brain structure in preterm infants (Valeri et al., 2015). Follow-up studies of former preterm infants without overt brain injury at school-age have found that stress exposure in the NICU significantly predicts the maturation of white matter (i.e. myelination) measured by diffusion tensor imaging (Vinall et al., 2014). Though stress exposure is not completely avoidable in the NICU setting, these detrimental experiences may continue to impact NICU patients long after they are discharged.

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Experimental studies in animal models support the findings of observational studies in human preterm infants and provide further evidence that early stress exposure negatively affects brain development and long-term outcomes. Studies using the maternal separation paradigm, a method commonly used to elicit stress responses in newborn animals, reveal that separation of newborn offspring from their mothers affects the offsprings' brain structure, including decreased hippocampal volume and neuronal density in the cerebral cortex (Aksic et al., 2013). In addition, novel protocols for animal models have been developed to simultaneously test the effect of maternal separation and multiple common NICU stressors – pain, light, noise, handling, cold stress, hypoxia – on brain function and mortality in animals (Huppertz-Kessler, Poeschl, Hertel, Unsicker, & Schenkel, 2012; McPherson et al., 2007). Findings from these studies reveal that exposure to common NICU stressors is associated with decreased early growth, increased mortality, and alterations in the concentration of neurotransmitters (Huppertz-Kessler et al., 2012; McPherson et al., 2007). Moreover, stress exposure is associated with altered brain growth (Smith et al., 2011), impaired stress responses (Cong et al., 2017), and poorer habituation to environmental stimuli (Cong et al., 2017).

Preterm infants in the NICU are exposed to numerous acute and chronic stressors throughout their hospitalization, including physiologic stressors (e.g. sepsis), experiential stressors (e.g. lab draws), and environmental stressors (e.g. excessive light, excessive noise) (Newnham et al., 2009). Examples of acute stressors include oropharyngeal suctioning, venipunctures, and intubation. These experiences may occur once or repeatedly over the course of hospitalization. Chronic stressors are those that are experienced over a long duration such as mechanical ventilation or sepsis (Newnham et al., 2009). A systematic review found that infants admitted to the NICU experience an average of 7.5-17.3 painful procedures per day and that lower gestational age at birth predicts a higher number of procedures (Cruz, Fernandes, & Oliveira, 2016). Research evidence reveals that environmental conditions and seemingly innocuous procedures, such as diaper changes and repositioning, can elicit stress responses in preterm infants (Peng et al., 2009; Zeiner, Storm, & Doheny, 2016).

Neonatal Stress Embedding Model

Theoretical Underpinnings

Our proposed model draws from the "Biological Embedding of Childhood Adversity Model", which posits that early life stress, in the form of childhood maltreatment and neglect and exposure to violence, results in an inflammatory phenotype that affects subsequent adult health outcomes (Miller, Chen, & Parker, 2011). Chronic, systemic inflammation results from epigenetic changes and inflammatory programming of monocytes and macrophages and a loss of inflammatory regulation through down-regulation of the glucocorticoid receptor.

The NSE model (Figure 1) expands upon these ideas and incorporates interdisciplinary concepts from the scientific literature on stress, neuroscience, molecular immunology, epigenetics, and developmental physiology. The NSE model provides a hypothesis-generating description of the mechanisms linking neonatal stress exposure and neurodevelopment in preterm infants. Similar to the "Biological Embedding of Childhood

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Adversity Model", the NSE model is based on the effect of early life stress on subsequent health outcomes. We theorize that stress-induced alterations to normal brain structure and function and subsequent neurodevelopmental impairments are the result of changes in functioning of the immune system, the autonomic nervous system, HPA axis, and gene expression.

Mediators of Stress Exposure and Alterations in Brain Structure and Function

Immune functioning.—There are limited data on the effect of chronic stress exposure on immunological functioning in preterm infants; however, evidence from adult studies has revealed that chronic stress responses are associated with systemic inflammation (Hansel, Hong, Camara, & von Kanel, 2010; Tian, Hou, Li, & Yuan, 2014). In such studies, systemic inflammation is operationalized through the measurement of cytokines and chemokines in the peripheral blood (Hansel et al., 2010). In studies of adults, work-related interpersonal conflict (Girardi et al., 2015) and daily stressors among adult caregivers (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012) are correlated with elevated levels of inflammatory biomarkers. These findings in adults have been replicated to a lesser extent in neonatal animal models. Studies of animal models demonstrate that neonatal stress induces an inflammatory phenotype in adolescent rats (Wieck, Andersen, & Brenhouse, 2013).

Stress-associated systemic inflammation is likely the consequence of two related phenomena: (1) the priming of immune cells, and (2) the loss of inflammatory regulation (Tian et al., 2014; Weber, Godbout, & Sheridan, 2017). Systemic inflammation may be increased through the priming of monocytes leaving the bone marrow. In response to signals from the sympathetic nervous system under conditions of chronic stress, the bone marrow preferentially upregulates the production of myeloid progenitors, which differentiate into activated monocytes that produce high levels of inflammatory cytokines and have increased phagocytic activity (Weber et al., 2017). Furthermore, animal models suggest that early life stress activates microglia, the primary regulator of immune responses in the brain, and results in an increased basal expression of the pro-inflammatory cytokines interleukin-1-beta and tumor necrosis factor-alpha in the hippocampus of mice subjected to maternal separation (Roque, Ochoa-Zarzosa, & Torner, 2016).

Primed monocytes exiting the bone marrow following sympathetic stimulation also appear to be resistant to glucocorticoid regulation (Weber et al., 2017). The glucocorticoid receptor is found in multiple cells of the immune system, including monocyte-derived tissue macrophages, neutrophils, and B- and T-cells. Under normal circumstances, binding of glucocorticoids to the glucocorticoid receptor in these cells suppresses the inflammatory response by preventing the transcription of inflammatory genes (Baschant & Tuckermann, 2010). However, glucocorticoid receptor expression is downregulated following social stress, which may result in a loss of inflammatory control (Jung et al., 2015). Downregulation of the glucocorticoid receptor and subsequent glucocorticoid insensitivity may be regulated by epigenetic mechanisms, including messenger RNA degradation by microRNAs (Jung et al., 2015). Loss of glucocorticoid receptor expression results in disruption of the negative feedback system that regulates systemic inflammation.

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Research findings have demonstrated that levels of some inflammatory factors are significantly negatively correlated with neurodevelopment in preterm infants (Kinjo et al., 2011; Kuban et al., 2015). These outcomes may be related to early brain injury associated with high levels of systemic inflammation (Korzeniewski et al., 2014). Using markers of neurological impairment, including abnormalities on cranial ultrasound or magnetic resonance imaging or depressed electroencephalogram activity, some researchers have associated inflammation with brain injury in preterm infants (Inomata et al., 2014; Korzeniewski et al., 2015; Wikstrom, Ley, Hansen-Pupp, Rosen, & Hellstrom-Westas, 2008). Similarly, investigators have found associations between markers of neonatal inflammation and long-term neurodevelopmental impairment, as measured by impaired behavioral, mental, and motor functioning (Kinjo et al., 2011; Korzeniewski et al., 2015; O'Shea et al., 2014).

Autonomic nervous system (ANS) functioning.—ANS responses to acute stressors have been studied in newborn infants (Weissman, Aranovitch, Blazer, & Zimmer, 2009) with results indicating that sympathetic nervous system activity is elevated during the stress exposure, as measured by increases in heart rate and low frequency to high frequency heart rate variability (HRV) ratios (Weissman et al., 2009). The effect of stress on sympathetic nervous system activity is modulated by non-pharmacologic interventions such as breastfeeding (Weissman et al., 2009) and skin-to-skin contact (SSC) (Cong, Ludington-Hoe, McCain, & Fu, 2009). In a study of the effects of noise stress on NICU patients, researchers found that patients exposed to loud noises had significant sympathetic nervous system activation, as measured by electrodermal responses and heart rate (Salavitabar et al., 2010). Importantly, repeated exposure to acute stressors in the NICU, such as a heelstick procedure appear to condition the ANS such that subsequent experiences elicit an increasingly robust response (Pineles, Sandman, Waffarn, Uy, & Davis, 2007). Preterm birth may alter the maturation of the ANS such that preterm infants have lower HRV than term infants, an effect that persists to at least six months of age (Yiallourou, Witcombe, Sands, Walker, & Horne, 2013). The effects of early stress exposure may continue into childhood, as alterations in baseline heart rate and stress-associated reactivity were present among former preterm infants with significant stress exposure in the NICU at 7 to 11 years of age (Goffaux et al., 2008).

Limited evidence on the effect of ANS dysfunction on short and long-term neurodevelopment in preterm infants reveals that decreased parasympathetic tone in the form of decreased HRV is predictive of future impairments. For example, decreased HRV accompanied by heart rate decelerations is associated with inflammatory conditions such as neonatal sepsis and significantly predicts the development of cognitive impairments and CP in very low birthweight infants (Addison, Griffin, Moorman, Lake, & O'Shea, 2009). Other researchers have confirmed these findings, demonstrating that lower HRV is associated with early impairments in coordination and significantly predicts the development of CP in term-born infants (Bjelakovic et al., 2010). Similarly, changes in HRV have been reported among preterm infants who later develop intraventricular hemorrhage (Tuzcu, Nas, Ulusar, Ugur, & Kaiser, 2009). However, the changes in HRV described above may only be markers of central nervous system alteration rather than a cause of later neurodevelopmental

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impairment. Further studies to determine the mediating effect of altered ANS functioning on neurodevelopmental impairment are needed.

Hypothalamic-pituitary adrenal axis.—Stress exposure appears to activate the infant HPA axis during a NICU hospitalization. In a study of term infants, researchers found that those admitted to the NICU because of birth related illness, had higher hair cortisol concentrations compared to healthy infants and that 21% of the variance in hair cortisol among the NICU infants was explained by the number of days that infants required mechanical ventilation (Yamada et al., 2007). Chronic stress exposure may affect the HPA axis, resulting in HPA axis fatigue and glucocorticoid resistance from repeated activation (Hansel et al., 2010; Tian et al., 2014). In a study of former preterm infants at four months of age, preterm boys had significantly lower salivary cortisol levels at baseline and following a stressor than term-born males, indicating alteration in stress reactivity and baseline functioning of the HPA axis (Grunau et al., 2010). Researchers have found that former preterm infants at school age also have lower hair cortisol concentrations than term-born children and that pain-related stress is a predictor of hair cortisol in preterm boys (Grunau et al., 2013).

Cortisol, the glucocorticoid product of HPA axis activation, may produce a pro-inflammatory response in the brain under conditions of chronic, unpredictable stress exposure (Duque Ede & Munhoz, 2016). By priming microglial cells and upregulating toll-like receptors, cortisol may mediate the production of pro-inflammatory cytokines following subsequent immune challenge, such as infection (Duque Ede & Munhoz, 2016). This may be important for preterm infants, who are exposed to significant stressors in the NICU and may experience concomitant or subsequent septic challenges.

Studies of HPA axis dysfunction and neurodevelopmental outcome are scarce, and more intense research into the long-term effects of altered HPA axis functioning in former preterm infants is needed. However, evidence suggests that these children have altered HPA responses to a standard laboratory stressor compared to term-born children as well as poorer memory and more emotional problems (Quesada, Tristao, Pratesi, & Wolf, 2014). Similarly, a study of seven year old term-born and preterm children found that among preterm boys, higher neonatal stress exposure was significantly negatively correlated with baseline cortisol levels which predicted attention problems (Brummelte et al., 2015). Further, a study of HPA axis functioning and behavioral outcomes in preterm infants found that children born preterm had a faster rate of cortisol decline in the evening compared to term-born children and that lower cortisol levels were associated with conduct problems in children at school-age (Perkinson-Gloor et al., 2015).

Gene expression.—Many of the mediators linking stress exposure and neurodevelopment described above are, in turn, mediated by changes in gene expression. The biological embedding of neonatal stress exposure on HPA axis functioning, for example, may be mediated by epigenetic changes to the genes regulating the HPA axis. Epigenetic changes to genes regulating HPA axis function have been demonstrated in animal models following neonatal stress exposure. Differential methylation of the glucocorticoid receptor promoter was observed in the hippocampi of pups born to attentive dams compared to those born to

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inattentive dams, a result that persisted into adulthood (Weaver et al., 2004). Other animal models have demonstrated that maternal separation during the neonatal period is associated with hypomethylation of the corticotropin-releasing hormone promoter, a downstream factor in the HPA axis, and hypersensitivity to stress (Chen et al., 2012). In human neonates, preterm birth is associated with significant changes in the methylation status of glucocorticoid receptor genes over the first four days of life, changes which are not found in term-born infants (Kantake, Yoshitake, Ishikawa, Araki, & Shimizu, 2014).

Changes in the epigenome during the postnatal period in preterm infants may also directly mediate the relationship between stress exposure and neurodevelopment. For example, researchers have found epigenetic differences between preterm and term infants in the genes coding neural functions (Sparrow et al., 2016). The differentially methylated genes identified by Sparrow et al. (2016) are responsible for a variety of neurologic functions and have been associated with neurodegenerative and neuropsychiatric diseases. In preterm infants, the serotonin transporter gene (*SLC6A4*) appears susceptible to methylation status changes over the course of hospitalization; these changes are subsequently associated with differences in infant temperament at 3 months corrected age (Montirosso et al., 2016). Further, NICU pain-related stress is associated with hypermethylation of the serotonin transporter gene, which predicts anterior temporal lobe volumes at term-equivalent age and socio-emotional functioning at 12 months corrected age in former preterm infants (Fumagalli et al., 2018). In animal models, epigenetic changes to genes in the rat hippocampus, which is important for memory and learning, following neonatal stress have been reported, further suggesting important neurodevelopmental consequences for changes in gene expression (Weaver et al., 2004).

Moderators of the Effect of Stress Exposure

Prenatal environment.—The extent to which neonatal stress exposure becomes biologically embedded to affect the physiologic systems described above may depend on the prenatal environment. For example, exposure to maternal cortisol, which is dependent on the placental 11βHSD2 enzymatic activity, may have consequences for neurodevelopment, including cognitive and motor development and stress reactivity (Hodyl et al., 2017). Significant research has focused on the impact of maternal prenatal stress on the behavioral health and neurodevelopmental outcomes of offspring. Animal studies have demonstrated that the offspring of pregnant rats exposed to restraint stress during gestation exhibited significantly elevated anxiety behaviors when exposed to stressors as adults and had elevated baseline circulating corticosterone levels compared to controls (Xu, Sun, Gao, Cai, & Shi, 2014). Similar findings have been realized in correlational studies of human prenatal stress. Infants born to mothers experiencing depressive symptoms during pregnancy had poorer self-regulation and more hypotonia during the neonatal period that those born to mothers without these symptoms (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013). A large study of over 700,000 children and 2 million adults found that exposure to prenatal stress, defined as maternal loss of a first degree relative or spouse during pregnancy, was associated with an increased incidence of autism spectrum disorder and attention deficit hyperactivity disorder among offspring (Class et al., 2014). Finally, a prospective cohort study examined the neurodevelopmental outcomes of children exposed to first trimester prenatal stress

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compared to controls matched on maternal demographics (Zhu et al., 2014). This study found that exposure to prenatal stress resulted in lower scores of cognition and poorer behavioral responses, controlling for gestational age, birthweight, and duration of breastfeeding. The same biological systems affected by neonatal stress exposure may be affected by the prenatal environment. For example, prenatal maternal stress has been found to negatively impact birthweight and methylation of the glucocorticoid receptor in neonates in a dose-response manner (Mulligan, D'Errico, Stees, & Hughes, 2012). Collectively, these findings suggest that neonatal physiologic responses to stress exposure may be moderated by the prenatal environment, which may result in programming of fetal systems *in utero*.

Maternal interaction.—The positive effects of maternal interaction, such as that experienced with SSC, in hospitalized preterm infants is well-studied. During SSC, the infant, wearing only a diaper, rests in a prone position on the mother's bare chest. SSC has profound positive effects for infant physiological stabilization and long-term cognitive development (Feldman, Rosenthal, & Eidelman, 2014). SSC may moderate the relationship between stress exposure and physiologic stress responses, as SSC decreases ANS responses to diaper changes and physiologic and behavioral signs of pain in preterm infants (Gao et al., 2015; Lyngstad et al., 2014). Further, maternally-administered massage or simple touch significantly reduces urinary cortisol in preterm infants (Asadollahi, Jabraeili, Mahallei, Asgari Jafarabadi, & Ebrahimi, 2016). Thus, maternal interaction may moderate the relationship between neonatal stress exposure and the physiologic stress responses, affecting the degree to which stress exposure becomes biologically embedded to affect neurodevelopment.

Practice and Research Implications

Implications for Clinical Practice

The optimization of neurodevelopmental outcomes is a priority for all clinicians caring for preterm infants. The NSE model suggests that reducing stress exposure might decrease adverse short-term effects on physiological functioning and long-term consequences for neurodevelopment. Consideration should be given to the type, frequency, and intensity of nursing care provided to preterm infants, as nurses are able to adjust care delivery to decrease stress exposure. For example, the method of bathing, the frequency of bathing, and supportive activities of the nurse during bathing may be adjusted to decrease infant stress responses without increasing the risk of infection or physiologic instability (Fernandez & Antolin-Rodriguez, 2018). In addition, nurses should attend to the assessment and management of pain during invasive procedures to modulate the intensity of these stressful experiences. Though neonates admitted to the NICU experience numerous painful procedures, especially in the first two weeks of life, pain management practices are inconsistent (Cruz et al., 2016), suggesting opportunities for improvement in nursing care that may improve neurodevelopment.

The complete elimination of stressors is not possible in the NICU; therefore, nurses should also focus on increasing maternal interaction (e.g. breastfeeding and SSC) to buffer the effects of stress exposure and reduce the extent to which stressful experiences become

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biologically embedded and affect neurodevelopment. Researchers have found that breastfeeding decreases behavioral and physiologic signs of stress in response to painful procedures (Weissman et al., 2009). Similarly, SSC is an evidence-based practice that increases physiologic stability (Chi Luong, Long Nguyen, Huynh Thi, Carrara, & Bergman, 2016), decreases stress responses (Gao et al., 2015), and improves long-term neurodevelopment in preterm infants (Feldman et al., 2014); however, significant organizational barriers and concerns regarding infant toleration of SSC limit nurses' facilitation of this intervention (Chan, Bergelson, Smith, Skotnes, & Wall, 2017; Kymre, 2014). Empirically-based rationales for the promotion of SSC in the NICU, such as that provided by the NSE model might increase rates of SSC, as educational programs for NICU nurses on the importance of SSC have increased nurses' competence in facilitating SSC and increased rates of SSC among mothers of preterm infants (Hendricks-Munoz & Mayers, 2014).

Implications for Research

In addition to these practice implications, the NSE model provides a hypothesis-generating, testable framework to develop interventions to reduce neurodevelopmental impairment and concepts to measure the intermediate effects of such interventions. According to the model, interventions that reduce the effects of stress exposure on immune functioning, ANS functioning, the HPA axis, and gene expression will likely improve neurodevelopment. In addition to interventions to buffer the effect of stress exposure on physiologic responses described above, pharmacologic and non-pharmacologic interventions may limit the effect of alterations in physiologic responses on subsequent neurodevelopment. For example, nutritional interventions to reduce systemic inflammation, such as glutamine or probiotic supplements (Keunen, van Elburg, van Bel, & Benders, 2015), may interrupt the causal pathway between stress exposure and neurodevelopmental impairment. However, such interventions require more rigorous testing.

Nursing research could also focus on developing interventions to promote neurodevelopment after the biological embedding of stress exposure in the NICU has occurred. Childhood represents a period of neuroplasticity, characterized by both developmentally-regulated and experience-dependent processes (Ismail, Fatemi, & Johnston, 2016). While neurogenesis is generally complete by the end of the second trimester, new synapses and synaptic pruning, which are sensitive to environmental influences, continue into early and middle childhood (Ismail et al., 2016). Interventions provided to high risk preterm infants during this time may be effective in moderating the detrimental effect of early stress exposure if they target the needs of each individual child. The Newborn Individualized Developmental Care and Assessment Program, based on Als' Synactive Theory of Development (Als, 1982), assesses preterm infants' capacities for self-regulation and physiologic stabilization in response to environmental stimuli and promotes relationship-based developmental care in the NICU (Als & Gilkerson, 1997). After discharge from the NICU, interventions similar to the Newborn Individualized Developmental Care and Assessment Program that enhance sensitive parenting and positive family processes, provide developmentally-appropriate sensory stimulation, and provide therapy based on individual needs may enhance neurodevelopment,

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though further testing and refinement of such programs during the post-hospitalization period are needed (Spittle et al., 2015).

Future research may examine the relationships proposed by the NSE model in greater detail. Research on the additive or multiplicative effects of alterations in the biological mediators may provide insight into the vulnerabilities of specific infants based on risk profiles. Though we have intentionally used a broad definition of neurodevelopment, alterations in specific biological processes may affect different aspects of neurodevelopment. Further, demographic and clinical variables may significantly moderate the effect of stress exposure on biological processes or of biological processes on subsequent neurodevelopment. For example, the effect of NICU stress exposure on future functioning of the HPA axis and stress reactivity may be moderated by infant sex given that males demonstrate greater vulnerability to aberrant HPA axis functioning than females (Grunau et al., 2013). Such interactive effects will be important to consider in the development of interventions, as infants may respond to interventions differently depending on demographic and clinical profiles.

Conclusion

The NSE model provides a comprehensive, theoretical description of the processes responsible for the biological embedding of stress exposure in preterm infants. Stress exposure in the neonatal period significantly affects long-term neurodevelopment, a phenomenon that may be mediated by changes in immune functioning, autonomic nervous system functioning, the HPA axis, and gene expression and moderated by the prenatal environment and maternal interaction. The NSE model could be used to test interventions that disrupt the pathways between stress exposure and neurodevelopment to improve long-term outcomes. In addition, the model provides a foundation to examine the person-level demographic and clinical variables that result in differential outcomes. Differences in race, genotype, maternal factors, and nursing care practices could be tested using the variables and relationships suggested by the model. The strength of the NSE model is its comprehensive description of the exact mechanisms responsible for the biological embedding of neonatal stress exposure, which provides specific target systems for novel interventions to attenuate or prevent the negative long-term neurodevelopmental consequences of early stress exposure.

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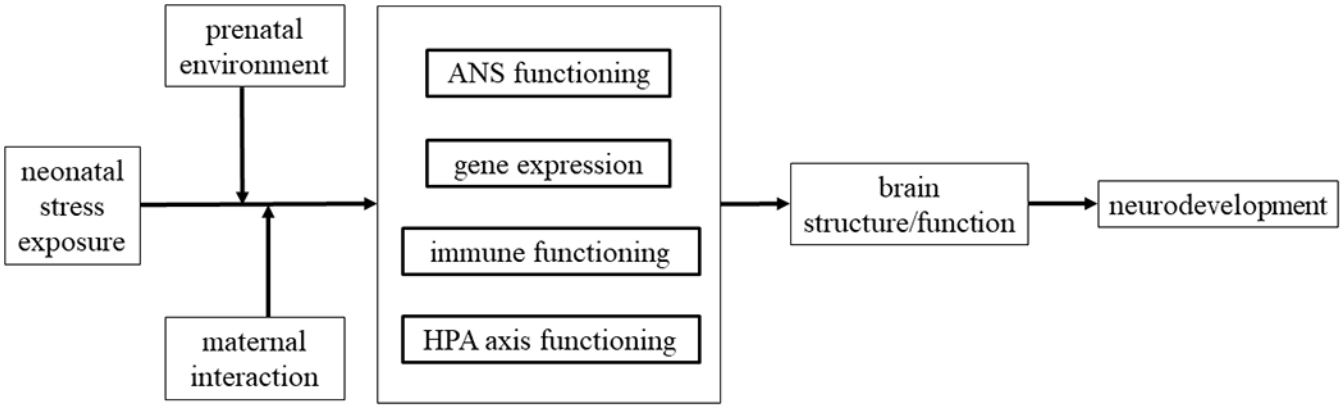

Figure 1.

Neonatal Stress Embedding model. The figure depicts the relationships among stress exposure, the affected biological systems, and neurodevelopment. The model posits that stress exposure during the neonatal period becomes biologically embedded to affect stress responses with long-term consequences for neurodevelopment. ANS = autonomic nervous system; HPA = hypothalamic-pituitary-adrenal.