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Infant Exposure To Potentially Traumatic Events In The Neonatal Intensive Care Unit

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Amy L. D'Agata, PhD

University of Connecticut, 2015

Infants who begin life in the medicalized environment of the neonatal intensive care unit (NICU) do so under adverse conditions. The NICU experience exposes infants to experiences that are different from well newborns. The impact these cumulative adverse conditions have on long-term neurodevelopment has yet to be fully elucidated, however the literature reveals a broad scope of later life challenges for former NICU infants. This dissertation focuses on several novel inquiries that may shed light on individual vulnerabilities. First, a framework of infant trauma is proposed to support improved understanding of the infant experience. Context is provided for the history of neonatal care, unmet expectations of newborns that require NICU care and opportunities for enhanced neurodevelopmental care. Next, the current NICU model of care is discussed from the perspective of a complex adaptive system framework. The complexities of NICU care and agents enmeshed within the system most influential to NICU outcomes; specifically parent, nurse and organization. Suggestions to incorporate parents as co-primary caregivers are offered. Lastly, is an investigation of stress-associated gene, FKBP5, and the potential genetic susceptibility to neurodevelopmental outcomes. Despite the small sample size, genetic susceptibility may be at play when considering how infants adapt to the stressful experiences of the NICU in relationship to neurobehavioral outcomes prior to NICU discharge. As a complete dissertation, these manuscripts provide evidence for a program of research focused on articulating the NICU infant experience and investigating the impacts of both the stress exposure in relationship to genetic vulnerability in the NICU.

Infant Exposure To Potentially Traumatic Events In The Neonatal Intensive Care Unit

Amy L. D'Agata

BSN, Saint Joseph University, 1998

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A Dissertation

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

at the

University of Connecticut

2015

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2015

APPROVAL PAGE

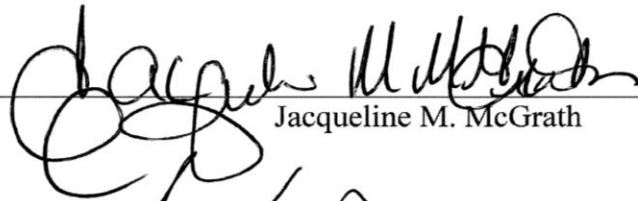
Doctor of Philosophy Dissertation

Infant Exposure To Potentially Traumatic Events In The Neonatal Intensive Care Unit

Presented by

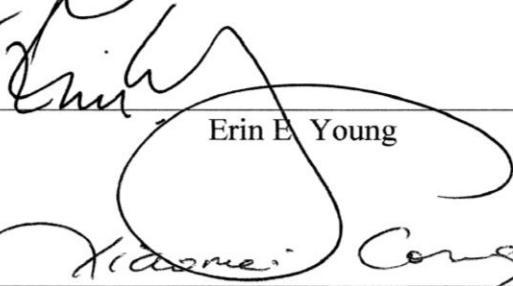
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2015

IT COULDN'T BE DONE

Somebody said that it couldn't be done,
But he with a chuckle replied
That "maybe it couldn't," but he would be one
Who wouldn't say so till he'd tried.
So he buckled right in with the trace of a grin
On his face. If he worried he hid it.
He started to sing as he tackled the thing
That couldn't be done, and he did it.
Somebody scoffed: "Oh, you'll never do that;
At least no one ever has done it";
But he took off his coat and he took off his hat,
And the first thing we knew he'd begun it.
With a lift of his chin and a bit of a grin,
Without any doubting or quiddit,
He started to sing as he tackled the thing
That couldn't be done, and he did it.
There are thousands to tell you it cannot be done,
There are thousands to prophesy failure;
There are thousands to point out to you, one by one,
The dangers that wait to assail you.
But just buckle in with a bit of a grin,
Just take off your coat and go to it;
Just start to sing as you tackle the thing
That "cannot be done," and you'll do it."

—Edgar Albert Guest

The village that supported me to accomplish my doctoral degree goal includes a broad scope of people, both professional and personal. Professionally, my academic advisory team and the School of Nursing faculty-at-large have assisted my growth in ways I never imagined. My major advisor, Dr. Jackie McGrath, has steadfastly supported every interest and idea I have had along the way and always helped me to figure out how to attain whatever I thought was important to my research goals. This was not always an easy task since the method of research that I wanted to learn and conduct was initially not available at the School of Nursing. That did not prevent Jackie from encouraging me to find the resources I needed to accomplish the work.

She has never failed to impart nursing and research experience and wisdom into every aspect of the task at hand. I will forever be grateful to have had the opportunity to learn from her.

Dr. Erin Young, an associate advisor, has become my genetics lifeline. I have learned so much from Erin in a relatively short period of time. She has encouraged me to stay true to the science of genetics and supported my growth in a number of ways. There have been days of just feeling lost and unsure I would ever master the science of genetics. While mastery will take years, I feel confident as I close the chapter of dissertation work that I have learned more than I probably realize. Recently I have been awestruck by the process of taking molecular laboratory data and translating those findings into practical, useful and powerful data that may benefit neonatal intensive care patients- this has truly been a life changing experience.

Dr. Xiaomei Cong, an associate advisor, has been a very important committee member as we share many common neonatal research interests. She has a very strong commitment to nursing science and has taught me valuable lessons that I will carry forward.

My other professional debts of gratitude go to my colleagues at Connecticut Children's Medical Center NICU. I have been a staff nurse in this unit on two separate occasions. I could have sought employment as a NICU nurse in a different hospital, however that never seemed to be an option for me as my heart has always belonged to CCMC. The team that I have worked shoulder to shoulder with are incredible people who truly strive to provide the best care possible to our patients. Over the last 3 years of juggling doctoral work with patient care, I have appreciated every word of support along the way- even when it wasn't always clear what I was working on. Finally, to Dr. Marilyn Sanders, thank you for all of our talks and ideas about how to improve the socio-emotional support provided to NICU babies and their parents.

As for my personal village, I would never have been able to complete this work without the support of my husband, Allen, and children, Molly Zachary, Owen and Olivia. They have never failed to support my professional growth opportunities, and there have been many, despite the constraints that may occur in the process. The five of you are the most amazing people and you all mean the world to me. Many thanks to my extended family and friends for all of your support and cheerleading. Lastly, thank you to my parents. I know that understanding this process has sometimes been head scratching for you but trust me it was all worth it. Thank you for always being willing to listen, being supportive and being proud. I feel like the luckiest person in the world to have such an amazing family, professional colleagues and a new career path ahead of me.

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CHAPTER 1.

INTRODUCTION

Introduction

Infants who begin their lives in the medicalized environment of a neonatal intensive care unit (NICU) have the potential for great divergence in long-term health outcomes. For instance, infants of similar gestational ages who have comparable courses of medical care in the NICU may have very different outcomes. This variability occurs despite fairly standardized protocols and regimented caregiving practices. Beyond mere states of health or illness, infants who require the more medicalized environment of the NICU after birth are exposed to adverse experiences, experiences that differ from what healthy newborns encounter. The adversities many NICU infants endure include intense and chronic experiences of stress, pain and parent separation. Following the elimination of prenatal factors as the cause of these differences, genetic variation may be a likely explanation.

Genetic variation describes individual differences within the genetic makeup (e.g. genotype) within and among members of a given population. One's phenotype encompasses the description of one's personal characteristics, both physical and behavioral, many of which are presumably related to an individual's unique genotype. For the purposes of the current discussion, it is important to remember that the most salient phenotype within the NICU is related to prematurity, which is not necessarily a reflection of the genetic makeup of the infant. However, we contend that specific genetic variation within the infant could present as a phenotype of stress resilience or stress sensitivity, which could then interact with adverse experiences in the NICU, to shape the neurodevelopmental trajectory of infants in the long term.

As previously noted, it is unlikely that the environmental impact of being cared for in the NICU is entirely responsible for the negative outcomes reported. Moreover, genetic susceptibility to stress and trauma may explain the variability in outcomes seen in preterm infants. In adult populations researchers have demonstrated associations between genotype and stress responses (Davydow et al., 2014). Since genotype is fixed across a lifespan for the individual, it is reasonable to conclude that genotype would influence the infants' response to this particular type of stress challenge.

Sensitive Periods of Development

Infancy is considered a sensitive period in development as negative experiences during this period may be particularly detrimental to long-term health due to the ongoing developmental processes. This is because the central nervous system and sensory organs that lay the template for both present and later neurodevelopmental function are still in critical periods of development. As neonatology continues to grow and develop as a medical specialty, it is clear this area of care is becoming better articulated in the decision-making surrounding care but there is still room for growth in this area. Thus, as medical care advances, the strain that care and the environment place on the central nervous system must become a more prominent clinical priority. For infants in the NICU, pain, stress and parental separation are ubiquitous and each of these has been shown to negatively affect a variety of health outcomes in both preclinical and clinical studies (Ranger & Grunau, 2014; Young et al, 2012; Lupien et al., 2009; Luchett et al., 2015; Nosarti, 2013). The intensity and chronicity these factors may have and the potential to expose infants to the types of medical trauma historically reserved for discussion in the pediatric and adult literature. Presently a gap exists, both in clinical

practice and in research, identifying and classifying the NICU infant experience as traumatic.

Framework of Infant Medical Trauma in the NICU (IMTN)

The development of this dissertation began with an interest in understanding the distinctive early life experience of infants in the NICU. As a mechanism to conceptually and visually elucidate the factors influential to NICU infants, we developed the model of Infant Medical Trauma in the NICU (**Figure 1**).

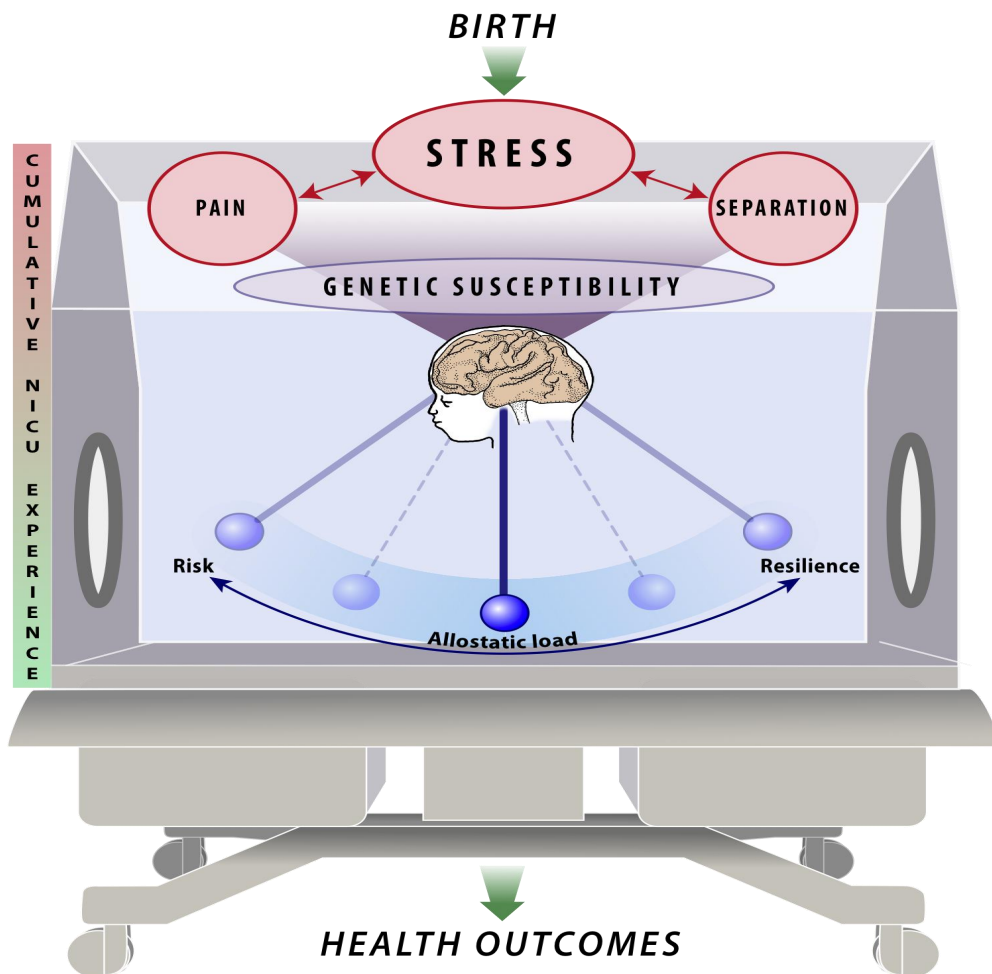


Figure 1. Infant Medical Trauma in the NICU.

The *Infant Medical Trauma in the NICU* model provides a framework for this dissertation by conceptualizing the potential developmental burden imposed by routine care in the NICU. Particularly unique to the NICU infant early life experience, as compared to a healthy term infant, are the negative sensory stimuli of pain and stress, as well as separation from parents. It is hypothesized that the intensity and chronicity of these factors may place infants at increased neurodevelopmental risk. While the greatest vulnerability for a traumatic experience likely correlates to the degree of prematurity, consideration is given to infants of all gestational ages who require NICU care as potentially vulnerable to a traumatic experience. It bears mentioning that the meaning and pervasiveness of an experience are individually and contextually driven, therefore some infants may be more susceptible to perceiving these experiences as traumatic than others. Simply stated, not all infants who are admitted to the NICU have the same experiences or responses to those experiences, and, even when circumstances are similar, individuals may have different outcomes.

Within the context of potentially traumatic experiences for infants cared for in the NICU, it is equally important to recognize the clinicians who care for these infants. A fundamental ethical and moral underpinning of clinical practice is to “do not harm”. This dissertation work does not question that principle and readily acknowledges the good intentions of clinicians; rather the focus of this work is concentrated solely on the experience of the preverbal infant and the potential burden from care on long-term health trajectories. It is our hope that, as this perspective is more broadly accepted, efforts will be made to enhance caregiving to improve health outcomes improvements for the most fragile of hospitalized patients.

Potential Outcomes of Preterm Birth

The outcomes from preterm birth today are notably different from outcomes just a few decades ago. Namely the incidence of significant neurodevelopmental impairments, such as cerebral palsy and intellectual disability, have decreased substantially. The longer-term outcomes former preterm infants face today are more nuanced behavioral, cognitive and mental health difficulties. While present day challenges are certainly less profound, they remain significant to the quality of life for affected individuals and are significant factors of financial burden to our educational and public health entities.

Social Interactions. Among the estimated 1 in 68 children diagnosed with autism spectrum disorder (ASD), the risk for autism may be 3 times higher for former preterm infants, particularly those who were born small for gestational age, low birth weight and infants with all grades of intracranial hemorrhage (CDC, 2014; Kuzniewicz et al., 2014; Pinto-Martin et al., 2011; Gardener et al., 2011). This increased risk is similar to findings in other recent studies that have reported a prevalence of ASD for preterm infants of 2% to 8%, a risk that is inversely related to gestational age (Abel et al., 2013; Johnson et al., 2010).

Attentional Deficiencies. An increased prevalence of ADHD has been described among former preterm infants, in some cases twice as many when compared to control groups (Hack et al., 2009; Lindström et al., 2011; Scott et al., 2012). Researchers have found that 20% to 30% of premature, very low birth weight or moderately low birth weight infants are estimated to have at least one mental health issue. By comparison, in the general U.S. population 15.5% of children have mental health problems (Singh et al., 2013). In this same study the mental health issues were largely explained by ASD,

ADHD and developmental delays, but statistically significant findings among depression, anxiety, behavioral conduct problems and prematurity were also reported (Singh et al., 2013).

Psychological/Psychiatric Issues. Several studies have demonstrated premature birth to be a risk factor for future psychiatric disorders, with higher prevalence rates of depression and anxiety found in young adults born extremely premature (Räikkönen et al., 2008; Johnson et al., 2010; Sullivan, et al., 2012; Grunau, 2013). Furthermore, when compared to term peers, children born extremely preterm have 4 times greater risk for anxiety disorders (Räikkönen et al., 2008).

Learning Impairments. For many former preterm infants, learning does not come easily. Relative to term peers, former preterm cohorts have been shown to perform significantly worse on all cognitive and academic domains, and display more severe responses on many behavior problem scales (Hutchinson et al., 2013). A linear relationship between gestational age and cognitive ability has been described, indicating that, as gestational age decreases so does long term cognitive ability (Poulsen et al., 2013). However, not all adverse preterm birth outcomes are experienced only by infants of the lowest gestational ages. Children born at 37-38 weeks, as compared with 39-40 week peers, also have demonstrated increased cognitive risks (Singh et al., 2013).

Overview of Dissertation Chapters

From the framework above emerged an opportunity to articulate the perceived infant experience as one of personal trauma. Furthermore, the underpinning of individual response to trauma has been linked to genetic susceptibility. One's genetic vulnerability to situations of extreme stress has been suspected as an important factor in determinants

of long-term mental health (Xie et al., 2010; Mehta et al., 2011). As such, Chapter 2 discusses the developmental vulnerabilities of this population as a basis for why distinctive terminology is needed for infants in the NICU. The evolutionary discrepancies of fetal-infant expectancies and genetic vulnerabilities are presented in relation to long-term health risks related to *Infant Medical Trauma in the NICU (IMTN)*. The burden of care that NICU infants endure is discussed within the context of unique neurodevelopmental sensitivities during infancy. Thus for the preverbal infant, ensuring care providers understand infant responsivity and behavior is critical to infant centered care. Suggestions for moderating the intensity of NICU infant experiences are outlined.

Utilizing a Complex Adaptive System (CAS) framework, Chapter 3 examines the interconnected relationships most influential to NICU infant outcomes. This chapter proposes a NICU model of care focused on improving neurodevelopment. In the dynamic environment of the NICU, it is proposed that active parent participation has the potential to decrease the intensity of pain, stress and parent-infant separation risk factors whereby by increasing infant resilience to adverse early life experiences. When considering how care is delivered in the NICU, our focus must not only be short-term survival but also on the long-term quality of life for each infant after infants complete medical care.

Given the significant individual variability in response to preterm birth and NICU, Chapter 4 is a primary research study exploring the genetic variability of stress associated candidate gene *FKBP5*. The main research question guiding this research was “Are neurobehavioral outcomes following extended NICU stay are influenced by FKBP5 genotype and cumulative stress exposure?” Because many infants exposed to the

stressful early life experience of the NICU show normal neurodevelopmental status and reach milestones as expected, it is unlikely that the impact of the NICU environmental is entirely responsible for the negative outcomes reported. As with many outcomes of complex etiology, it is the interaction of innate (genetic) and environmental factors that shapes our developmental course. In the harsh environment of the NICU, genetic susceptibility to stress and trauma is a likely candidate for explaining the variability in outcomes seen in preterm infants.

Together these three chapters present intricate exposures of where gaps in the neonatal science currently exist and attempt to fill those gaps. By revealing the lack of existing terminology specific to the unique needs of highly vulnerable newborns that require prolonged medical care, this work offers: the proposal a term has the potential to validate infants' experiences, create a common language for healthcare staff and families; begin to identify clinical practice interventions to minimize the negative impact of NICU care; and, commence investigation of possible genetic influences of stress exposure to traumatic experiences in the NICU.

Introduction Summary

All experience is modified by genetic predispositions. For some individuals, within their genetic context, adverse experiences may result in increased vulnerability or possibly resilience. The advent of modern neonatal care allows for infant survival from earlier gestational ages, however standardized NICU care has not evolved to a state of fundamental infant-centered care. While many infants exposed to stressful early life experiences of the NICU show normal neurodevelopmental status and reach milestones as expected, all do not. During the NICU experience infants may be exposed to

extraordinary experiences of stress, pain and separation; experiences that differ vastly from the healthy newborn. Given the accumulation of evidence articulating how profound early life influence is to infant health trajectories, providers of neonatal care must consider both language that acknowledges the infant experience and mechanisms designed to deliver better supportive care.

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CHAPTER 2

Unpacking The Burden of Care for Infants in the NICU

Unpacking The Burden of Care for Infants in the NICU

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Abstract

Infants who begin early life in the medicalized environment of the neonatal intensive care unit (NICU) experience disruption to numerous fundamental expectancies. In the NICU infants are often exposed to chronic, extreme stressors, including painful medical procedures and parental separation. Due to their preverbal stage of development, infants are unable to fully express these experiences and linking these experiences to long-term outcomes has been difficult. In this clinical paper, a review of the Infant Medical Trauma in the NICU is discussed. Followed by a brief history of neonatal intensive care. Next, the unique and critical factors that define the newborn period expands the IMTN are explored. Then an interpretation of infant responsivity and behavior are reviewed. Additionally, an integration of the long-term impact of adverse events in childhood is provided. Finally, suggested recommendations for providing neuroprotective strategies for moderating the intensity of NICU infant experiences are outlined.

Unpacking The Burden of Care for Infants in the NICU

Overall early life provides a roughly ordered sequence of developmental windows of opportunity that, in turn, allow both mundane and extraordinary experiences to get under the skin at strategic time points to alter specific biological functions, which, in turn, have the capacity to alter life course trajectories.

Hertzman, 2012

There is a void in our medical lexicon to describe the unique experience of infants who require early life medical care in the Neonatal Intensive Care Unit (NICU). Infants who begin life in this medicalized environment are often exposed to chronic, extreme stressors, including painful and unpredictable medical procedures and prolonged separation from parents. Although inherited genetic susceptibility and the health of the prenatal uterine environment provide a foundation for the neurodevelopment of the fetus, the infant's interaction with the environment soon after birth is no less critical to both early and long-term development. Consequences of these early, stressful experiences, while incidental to essential medical treatment, and often unrecognized by staff, may be profound.

In the 1970's Als, Brazelton and others began to describe infant behavioral cues, shedding light on the infant experience; yet the translation of this critically important work as a guiding force to caregiving remains inconsistently implemented across NICUs (Als et al., 1977). Both the interpretation of the preverbal infant's language and delivery of developmental care are inconsistent practices (Coughlin et al., 2009; Coughlin, 2014). Most neonatal clinicians are not trained to decode the language of the preverbal infant. Interpreting this language requires both a commitment to listen and the development of

new skills beyond those typically taught in medical or nursing training. For those practicing in the NICU it is often easier to provide caregiving from a task-oriented approach. The overall goal of this manuscript is to examine through a philosophical lens the language used to describe the experience from the infant's perspective. Without a common language to describe an experience that is owned by preverbal individuals, we are limited in conceptualizing and advocating for improvements to care that acknowledges their unique experience.

The traumatic experience and sequelae of preterm birth as experienced from the parental perspective (Forcada-Guex et al., 2011; Lefkowitz et al., 2010) has been described; however, little attention has been paid to the infant – the direct recipient of these medical procedures. While describing the preverbal developmental stage of the infant experience is challenging, infant providers and investigators must surmount this barrier. We propose *Infant Medical Trauma in the Neonatal Intensive Care Unit (IMTN)* as a framework for understanding the needs of these infants in the clinical setting. Following a review of the IMTN framework, the paper is organized into five sections. First, a brief history of neonatal intensive care is presented. Second, exploring the unique and critical factors that define the newborn period expands the IMTN discussion. Third, interpretation of infant responsivity and behavior are reviewed. Fourth an integration of the long-term impact of adverse events in childhood is provided. Finally, suggested recommendations for providing neuroprotective strategies for moderating the intensity of NICU infant experiences are outlined.

Infant Medical Trauma in the NICU

Trauma is a word of Greek origin, defined as ‘to wound’. In the context of IMTN, trauma represents interconnected early life NICU experiences (e.g. stress, pain and parental separation). Both physical and socioemotional aspects may compromise infant neurodevelopment. Rather than a clinical diagnostic term, trauma is intended to represent the gestalt of the infant experience. This is informed by, but distinct from, trauma in the context of posttraumatic stress disorder (PTSD) where a potentially traumatic event is defined as direct or indirect exposure to death or threatened death, actual or threatened serious injury, or actual or threatened sexual violation (APA, 2013). We operationally define IMTN as the intertwined and cumulative early life experiences of stress, pain and parental separation that occur in conjunction with or as a consequence of medical care and that may affect short and long-term neurodevelopmental and physiological responses.

Infants come to the NICU with a well-established foundation that includes their biologic endowment, genetic susceptibility and interactions within the fetal environment (**Figure 1**). The biologic endowment is a combination of both the brain morphology and structural foundation as well as the neurobiophysiological responsivity of the fetus/infant within the fetal environment. Genetic susceptibility provides a foundation for how the brain will respond to stressors throughout the lifespan. These formative components although very important are not modifiable by caregivers in the NICU and thus, the focus of care must shift towards factors that we do have the potential to influence. The human template of the vulnerable newborn is dynamic, and in a free flow interchange with subsequent experiences within the NICU environment. It is not immutable. Our

framework for Infant Medical Trauma in the NICU (**Figure 2**) illustrates significant adverse exposures infants encounter in the NICU. As discussed in D'Agata et al. (under review, 2016), these factors may represent the most prominent negative events NICU infants encounter, as compared to healthy newborns cared for in a well nursery. Infants who begin life in the NICU are often exposed to chronic, acute and unpredictable stressors, such as painful medical procedures as well as prolonged separation from parents. Each aspect of the framework is briefly described below.

Stress. A stressor is an actual or potential disturbance to one's environment (Joels & Baram, 2009). In this framework, stress is an umbrella variable, both independent as well as interdependent with other variables. As an independent factor, infants encounter many stressors including environmental factors such as extreme light, loud noises, and unpredictable caregiving provided by multiple caregivers. The environment is not at all what the preterm infant is prepared to encounter and as such the infant is often at the mercy of the environment.

The unpredictability of NICU stress is intertwined with many aspects of caregiving. For example, infants may be unable to discriminate between painful and non-painful touch until 35-37 weeks post-menstrual age (PMA). While touch is inherent to physical interactions, as well as the developing infant's physiological stress response system, a newborn's inability to anticipate touch makes it an unpredictable phenomenon (Feldman et al., 2010; Fabrizi et al., 2011). This also suggests intrusive caregiving disruptions may not be easily discriminated by the infant from nurturing touch. Thus, many invasive and noninvasive caregiving tasks, including parental touch, may be perceived as stressful by the infant. Considering the state of infant brain immaturity, the

lack of touch discrimination, and the duration of stressful and painful medical care, these experiences may contribute to unpredictability. As an interdependent factor, stress is interwoven *within* both the variables of pain and separation.

Pain. Pain is defined as the unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms as damage (IASP, 1994). Regardless of age, pain is a side effect of many procedural interventions in healthcare. The unpleasant and unpredictable nature of pain in the NICU results is stress recognized in disengagement behaviors and poorer autonomic responsivity (Grunau et al., 2005). The challenges in recognizing pain and stress historically has led to many false assumptions, For example, that infants, especially preterm infants, did not experience pain due to their neurologic immaturity (McGraw, 1941; Rodkey & Pillai Riddell, 2013). Ironically, later research indicates that preterm infants often suffer from hypersensitivity to pain (Slater et al., 2010; Valeri et al., 2014). Based upon animal models, this may occur due to cutaneous hyperinnervation, the retraction of which occurs postnatally over time and hyperexcitability or hypersensitivity within pain processing pathways (Fitzgerald, 2005). Simply put, the interaction of pain with an immature and still-developing nervous system changes the neuro-pathways.

Parent-Infant Separation. Infants born very early or with significant anomalies may require weeks or month of hospitalization. Therefore the opportunity for parental connectedness may be significantly impacted by the degree and duration of NICU care that is required. As a consequence, infants may experience alterations in parental attachment (Shah et al., 2011).

It is important to remember that early life human connectedness lays the foundation of social and emotional development and mental health throughout the lifespan (Bowlby, 1979). Infants are born with an array of intrinsic attachment behaviors aimed at seeking and maintaining proximity to attachment figures, typically parents (Bowlby, 1988). Since infants cannot survive without caregiving, the purpose of proximity seeking is believed to support and protect an individual and ease distress (Mikulincer et al., 2003). For the infant, successful accomplishment of proximity results in attachment security. Maternal deprivation occurs when an infant or child lacks physical or emotional proximity to the attachment figure (Bowlby, 1952). The independent and cumulative effect of these variables (stress, pain and separation) may play a role in an infant's phenotype, resulting from both gene x environment interactions and allostatic load. In fact, the an infant's genetic susceptibility may help explain why some infants have poorer outcomes than others.

Genetic Susceptibility. Considerable variability exists in the cognitive and social outcomes of infants cared for in the NICU. Some infants emerge from the experience without any appreciable deficits, while others experience profound deficits even when their courses seem similar. Within and among people in a given population are a host of noticeable individual differences (e.g. appearance, behavior, cognitive ability, emotional regulation); these differences originate from our genetic variation or genotype. While our genotype is fixed across the lifespan, environmental factors can interact with our genes leading to phenotypic variability, including differences in physical and behavioral characteristics. Of great interest to this conceptual model may be the environmental interaction with stress-related genes.

Allostatic Load. Allostasis is a maintenance mechanism for our homeostatic systems. It is a self-righting mechanism, allowing the body to maintain stability through change. The primary mediators of allostasis include hypothalamic-pituitary-adrenal (HPA) axis hormones, autonomic nervous system and cytokines (McEwen, 2005). When homeostatic systems extend beyond their limits the imbalance is considered in an allostatic state. Allostatic states can be maintained for discrete periods of time; however sustained imbalance results in wear and tear on regulatory systems. The cumulative effect of allostatic burden is often referred to as allostatic overload. As unique entity, allostatic overload serves no purpose, however, the increased stress ultimately leads to disease susceptibility (McEwen, 2005).

The intensity and chronicity of stressful experiences may drive the degree of impact on infant development. For NICU infants this likely includes their exposure to stress, pain and parent separation. Experiences may be further amplified by fetal programming, the state of infant vulnerability and underlying genetic susceptibilities. Given the enormous number of potential risks NICU infants face, care must be oriented towards neuroprotection and moderating those experiences.

Brief Epidemiology of Neonatal Intensive Care

As a means for better understanding the above framework, it is important to have a foundation in neonatal intensive care. In a typical, healthy pregnancy the developing fetus is cared for and protected within the mother's womb to allow for full growth potential and optimal positioning for extrauterine life. Now consider a birth that occurs too early or one that is compromised by an ill-born infant. Immediately following birth, approximately 10 percent of all newborns require medical intervention in a neonatal

intensive care unit (Kattwinkel et al., 2010). As a pediatric subspecialty, neonatology is a young field. In 1965, the first NICU was established in the United States and as recently as 1975, physician board certification in neonatology was established (AAP, 2001). High survival rates are now common with the application of technologies used in older patients that are scaled down to accommodate smaller and more vulnerable patients. With improvements in neonatal resuscitation and technology, potential infant viability is generally considered just beyond mid-pregnancy (Higgins et al., 2005). At this stage of fetal development infants have gelatinous skin and fused eyes. Infants are unable to independently breathe, eat, or maintain thermoregulation (Cloherty et al., 2008). While organ systems develop with each week post-birth, before 32-33 weeks gestation, most infants require considerable medical support to maintain the most basic functions (Cloherty et al., 2008). The life-saving procedures necessary for each infant may range from minimally to highly invasive, painful, and stressful. With all of this success however, the morbidities for NICU graduates far exceed term population.

What is Unique About the Newborn Period?

Since infants may be admitted little more than halfway through pregnancy, the stresses of the NICU environment are overlaid on critical periods of an immature and a rapidly developing central nervous system. To the average person a preterm infant may appear to be a little more than a pint sized term infant, as outwardly all anatomical components are present. This misleading perception fails to include the gravity of pregnancy interruption that has occurred. Of paramount concern, the central nervous system and sensory organs, that lay the template for both present and later neurodevelopmental function, are still in critical periods of development.

It is the input of both ubiquitous and unique environmental experiences, occurring in utero and postnatally, that influence neural organization and adaptation (Greenough et al., 1987). Following embryonic development, gestational weeks 9 - 40 represent the fetal period of brain development; for a detailed review see Stiles and Jernigan, 2010.

Evolutionarily, the fetal period of neurodevelopment relies upon systematic brain maturation, through both gross anatomical and microscopic cellular processes (Hruby et al., 2013). In the central nervous system, less may be more as activity-dependent synaptic connections, allow for the natural pruning of less active or developed neurons (Hua & Smith, 2004). The enduring synaptic connections result from repeated activity, thus forming neuronal pathways, which allows for the development of memory, learning and behavior (Hua & Smith, 2004). Although this neuro pruning is normal in the prenatal period it is easily altered by the experiences the infant encounters and once altered it is not easily righted and as such development overtime is also altered.

Moreover, the experience of the NICU infant occurs concurrently with what should have been the orderly progression of CNS development outside the environment of fetal expectancy- the mother's uterus. The infant expectancy immediately following birth is to transition from the womb to the mother's body for both protection and nurturance. However, for the developmentally vulnerable infant requiring medical care after birth, the infant is physically and emotionally separated from their mother. This separation coupled with the experiences of discriminatory touch leaves the infant in a heightened state of susceptibility to environmental experiences. From a developmental perspective, NICU admission presents as a violation of expectancies for both the infant and the family. It is important to remember that during sensitive periods of early life

brain maturation, developmentally unexpected sensory experiences may influence subsequent central nervous system function (Fitzgerald, 2005; Ranger & Grunau, 2014). Thus, until neural circuitry maturation, infants may be at risk for overexposure to multiple types of sensory stimuli or stressors. Furthermore, the duration of endured stress, typically defined as a week or more in the animal model, may evoke a state of chronic stress with potential to impact early and long lasting neuronal development (Joels et al., 2007; McEwen, 2007).

Recent research has confirmed a relationship between children between the early caregiving environment and the stress response system. As evidence in children exposed to prolonged institutionalized care, early placement in foster care significantly improves the potential for blunted cortisol and autonomic responsivity (McLaughlin et al., 2015). This provides evidence, in humans, of a sensitive window of development in which the environment may alter the stress response system. Considering the plasticity of the infant brain, attention to neuroprotective and supportive care during and following medically necessitated institutionalized care is critically important to long-term health (Gluckman et al., 2011; Marsac et al., 2014; McEwen & Gianaros, 2011). It is therefore important for caregivers to understand infant behavior and autonomic responsivity.

Infant Behavior and Autonomic Responsivity

Infants communicate their adaption of stress exposure through behavioral and physiologic mechanisms. While the infant's preverbal stage of development may be a challenge, the clues are there for the attentive care provider, observer or investigator. Biological embedding describes experiences during sensitive periods of development that "get under our skin" (Hertzman, 2012; Fox et al., 2010). These influential sensory

experiences activate genes in areas of the brain that then commit differentiating neurons to sensory functions, establish sensory pathways ultimately leading to neural and biologic pathway determination (Hruby et al., 2013). Thus adverse experiences may shape brain development, potentially resulting in abnormal neurodevelopment (<http://developingchild.harvard.edu>, 2014). For example, the experience of pain in the NICU may have implications for the development of biological stress systems. Given the frequency and potential duration of painful procedural encounters, an average of 12 painful procedures per hospitalized day, the opportunity exists for long-term effects (Carabajal et al., 2008).

Grunau et al. have demonstrated that infants exposed to higher levels of pain in the NICU have altered autonomic responses to painful events. The directionality seems to relate to timing of the insult and the degree of prematurity (Grunau et al., 2001a, 2004, 2005, 2007). Extremely preterm infants, who had experienced long term NICU chronic and acute pain, assessed at 32 weeks PMA demonstrated blunted cortisol response to stress (Grunau et al., 2005). Conversely, during late infancy, former NICU infants have an up-regulation of cortisol response to stress (Grunau et al., 2001b, 2015). These age-related stress responses potentially demonstrate a “resetting” of the stress response system as a result of early life pain experience (Vinall et al., 2014). For former very preterm infants at school age, associations have been found with inferior cognitive outcomes and smaller cerebellar volumes and increased procedural pain in the NICU (Ranger, 2015). Similarly, former very preterm infants who experienced increased invasive procedures have alterations in brain white matter and lower IQ (Vinall & Grunau, 2014).

Impact of Adverse Events of Childhood on Later Health and Development

The association between decreasing gestational age, birthweight and diminished cognitive and psychological outcomes is well established. Both former early preterm and extremely low birth weight infants demonstrate poorer cognitive ability and increased incidence of behavioral difficulties (Hutchinson et al., 2013; Johnson et al., 2009; Johnson et al., 2010; Lindstrom et al., 2011; Marlow et al., 2007; Scott et al., 2010). However, decreased cognitive ability, compared to term infants, is also seen in late preterm infants and early term infants (Poulsen et al., 2013). Even with maturation, these children continue to have cognitive and behavioral challenges well into adolescence and adulthood (Lahat et al., 2014; Sullivan et al., 2012). Even though one could argue that prematurity alone could be the best predictor, numbers of days in the NICU is also associated with worse neurodevelopmental outcomes (Jarjour, 2015).

Brain volume, alterations in microstructure and white matter injury are all associated with diminished neurodevelopmental outcomes (Bora et al., 2014; Chau et al., 2013; Kidokoro et al., 2014; Munakata et al., 2013; Smyser et al., 2013; Thompson et al., 2014; Wisnowski et al., 2014). Smith demonstrated that increased stress exposures in the NICU were associated with decreased brain size and alterations in the brain microstructure and functional connectivity (Smith et al., 2011). Both white matter injury and time impaired brain microstructure were significantly associated with poorer early cognitive and language outcomes (Chau et al., 2013). As a result, these scientists suggest the need for a brain injury paradigm shift from a fixed lesion model to one that reflects the potential for evolving injury over the course of care.

From a broader epidemiological context, NICU infants constitute a subgroup of the childhood population, a group identified as at risk for trauma exposure (Finkelhor et al., 2013; U.S. DHHS, 2013). The cumulative effects of adverse childhood events are contributory to increased risk for poor mental health outcomes (Putnam et al., 2013). For some children their adverse early life experience of being cared for in the NICU *may be* the initial stimulus that heightens their lifetime risk. Thus, NICU infants who experienced early life trauma in the NICU and subsequently experience childhood maltreatment, may be increasingly vulnerable.

How Can We Improve Early Experiences for the NICU Infant and Family?

For both infants and parents care in the NICU, while promoting survival, represents an interruption to many beginnings. Knowing that a healthy infant's extra-uterine life does not normally include intense and prolonged experiences of pain and stress, strategies for improvement include:

Provision of a Common Language. First and foremost, acceptance of terminology to describe the infant experience is needed. These vulnerable and preverbal newborns have the basic human right to have their intense and prolonged experiences of stress, pain and separation validated through language. In turn, this language will be critical to assist caregivers, both family and professional, to recognize and communicate about the perceived infant experience. Once our language can both name and validate the infant experience, how can our care delivery model truly better support these infants? This calls to action those who can influence the NICU model of care worldwide, includes clinicians, parents, administrators and organizations, to redesign care to be truly neuroprotective and infant-centered care.

Objective Measure of the Cumulative Stress Exposure. To support clinicians' and parents' awareness of an infant's cumulative daily stress exposure, the development of a stress measurement score, similar to pain measurement scores will allow us to quantify exposure. We now utilize pain measurement scales to assist with physiological and behavioral signs and symptoms of infant pain (Cong et al., 2013). Of similar need in clinical practice is a mechanism to evaluate infant stress experiences. The development of an infant stress scale to capture the essence of an infant's experience, ideally situation within the electronic medical record, will assist clinicians to assess infant response to cumulative stressors. In conjunction with research exploring when stress exposure becomes detrimental, the stress score and their corresponding risk categories, may allow clinicians to modify the environment or timing of procedures and to be neuroprotective with provision of necessary infant rest.

Provision of Support for the Central Infant/Parent Relationship vs. Infant/Professional Relationship. The innate desire of an infant is for close proximity to his/her parents for protection and nurturance. This proximity can be restricted in the NICU because of medical technology limitations and/or infant health status. Furthermore, rather than considering parent contact and holding as a supportive health intervention, in the clinical setting, infant holding may be considered as stressful and an interference to medical care. A recent study by Hendricks-Munoz et al. discovered a significant difference between how nurses and mothers related to the perceived importance of parental presence in the NICU. Of the nurses surveyed, only 21% reported parental presence to be important as opposed to 67% of mothers. Additionally, 90% of mothers saw themselves as needed care members while only 40% of nurses agreed with this statement (2013). It is

concerning to consider that parents may perceive these beliefs held by some clinicians, see D'Agata et al. (Chapter 3, under review) for further discussion.

Most infants in a single unit study were visited by their parents 5 days or less per week, with a median 14 hours per week (Reynolds, 2013). This represented 5% of the total time the infants were cared for in the NICU. However, higher frequency of parent visitation and holding was highly correlated with improved neurobehavior at discharge (Reynolds et al., 2013). Early intervention to facilitate parent attachment potentially has lifelong health benefits, particularly related to mental health and stress outcomes (Fan et al., 2014; McLaughlin et al., 2015). This is outcome is not about the parents and making them feel part of the infant; it is about the infant making them feel part of the parents.

Another promising intervention is family-integrated care, where parents of recovering preterm infants provide significant care, beyond the simple tasks commonly allowed for parents (e.g. diaper changes, temperature measurement, feeding, etc.). Engaging, assisting and educating parents to care for their infant, even during semi-acute stages of illness, may support parents in a number of ways. First, during acute stages of illness parents learn normal versus abnormal assessments, which benefit parents beyond the NICU stay. Next, parents are able to offer their infant comfort during caregiving, which can be less stress provoking for some infants. Finally, facilitation of parent hands-on care provides another opportunity to promote infant-parent attachment and support parents to feel they have a meaningful role in helping their infant in the journey to health and wellness (Jiang et al., 2014).

Learning From Other Research. The social-emotional experience of early life in medicalized environments shares similarities to orphaned children placed in early life

institutional rearing environments. While associations between NICU care and institutionalized care are not commonly discussed, parallels exist between these caregiving environments (e.g. multiple caregivers, rotating shifts of caregivers, ratio of child-to-caregiver, and limited individualized care (Bick, 2015). Developmental outcome deficits for children reared within institutional environments in physical growth, cognitive, emotional and behavioral domains are demonstrated (Bakersman-Kranenburg et al., 2011; Smyke et al., 2007). Of note, the infant participants in these studies did not experience the painful procedures typical of a medicalized environment, yet still suffered significant psychosocial deficits. These results caution us that infants or children cared for in any institutional environment need significant attention to provision of positive early life caregiving experiences as well as environmental care modifications (Drury et al., 2012; McGoron et al., 2012).

Future Research

Important considerations for future research include further investigations of NICU environmental factors influential to the long-term health. Presently, many NICUs have chosen single room designs to support both infants and families. More research is needed to understand the long-term neurodevelopmental outcomes of infants cared for in these units. Using a stress measurement instrument, is infant stress in a single room design different from open bed designs? What are the long-term differences in outcomes? How can meaningful parental presence be measured? Is meaningful parental presence different based on the design of the unit? Moreover, what is meaningful parental presence and how can it be best be encouraged and supported?

At this time, within NICU caregiving, a comprehensive measurement of one's allostatic load does not exist. Additionally, factors influencing the health of a NICU infant (stress, pain and separation) are not all captured by current assessment methodologies. While in clinical practice the perception of infant pain is measurable through the use of pain scores, stress and parent-infant separation are not. As can often occur in clinical practice, when an outcome is unable to be measured it may dismiss it as unimportant. However, given the breadth of research presented in this article, lack of attention to the NICU infant's risk factors may place infants at risk for negative long-term health outcomes. The development of mechanism to measure influencing factors may be critically important to improving the neurodevelopmental health of infants.

Infants are unable to articulate to caregivers the extent of their pain and stress burden or their need for human connection. This lack of communication may result in experiences that would not occur if the patient were verbal and able to self-advocate. Additionally, infants in the NICU are subjected to repeated negative experiences that may impact their long-term development. Universally, clinicians in the NICU are focused on providing the best care possible to support infant health and development, however improvements to clinical care typically only occur when science demonstrates evidence of a better way to practice. The time has come for clinicians and researchers to focus on the multidisciplinary science of understanding inadvertent infant trauma in the NICU and conduct research focused on the neurodevelopmental implications of care in the NICU. The acceptance of a term to describe the NICU infant experience will allow for common language both in practice and research, as well as a critical avenue for scientific inquiry

with limited research despite profound importance for patients, families and public health.

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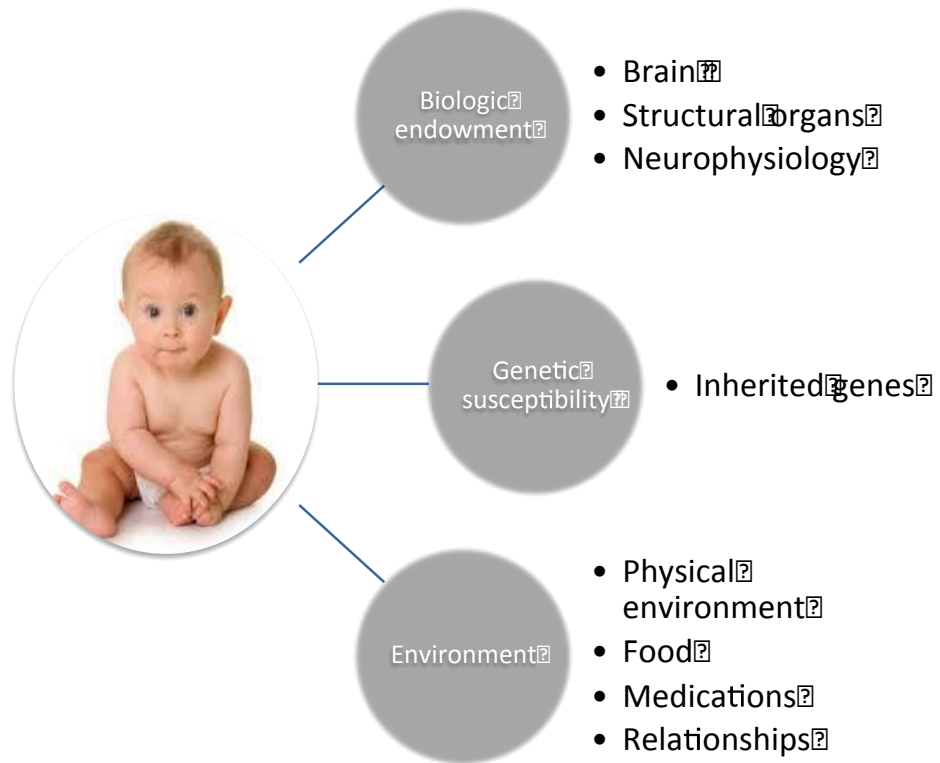
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Figure 1. The human template.



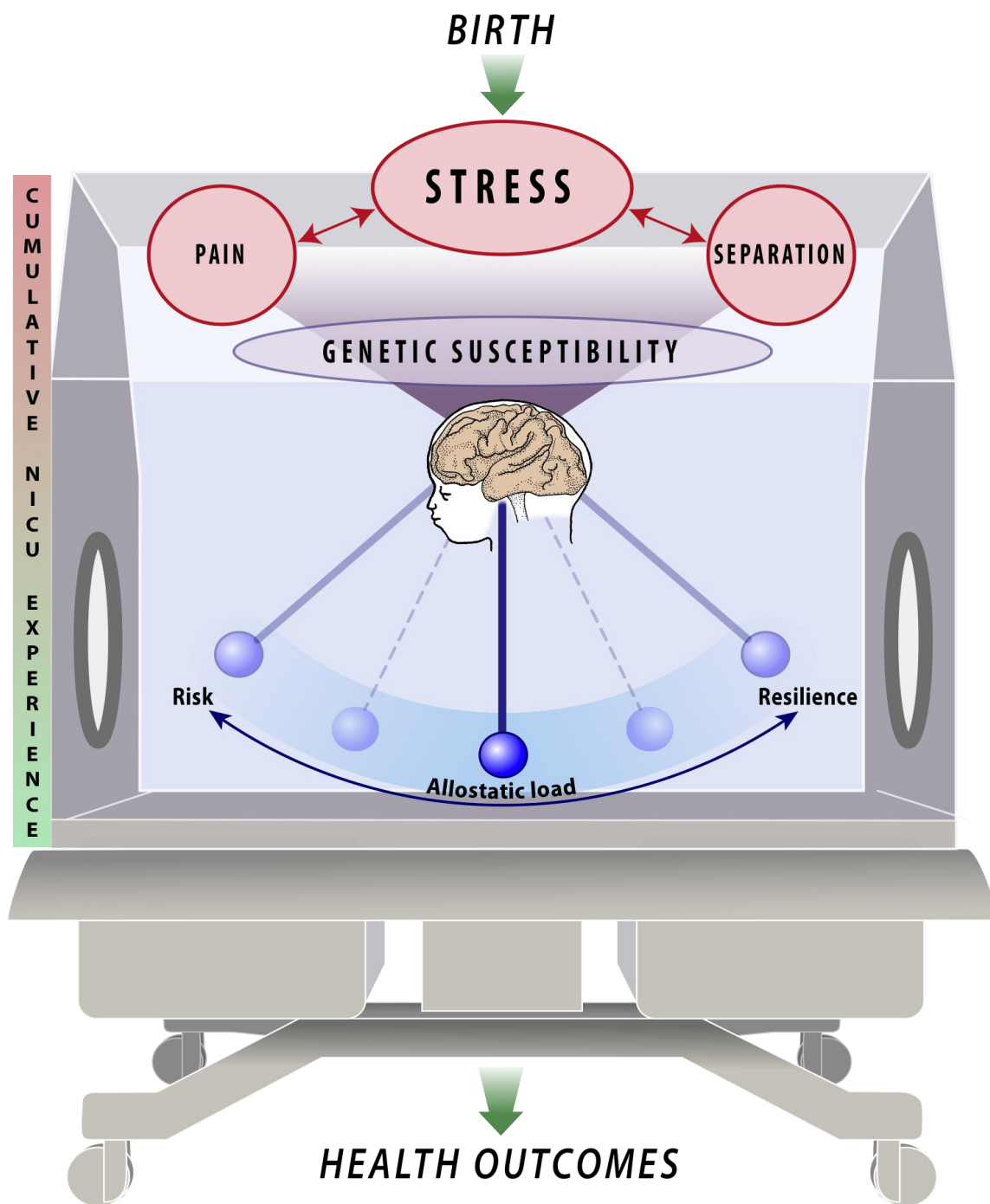


Figure 2. Infant Medical Trauma in the NICU model.

CHAPTER 3

A Framework of Complex Adaptive Systems: Parents As Partners in the NICU

A Framework of Complex Adaptive Systems: Parents As Partners in the NICU

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Abstract

Advances in neonatal care are allowing for increased infant survival, however neurodevelopmental complications continue. Using a complex adaptive system framework, a broad analysis of the network of agents most influential to vulnerable infants in the Neonatal Intensive Care Unit (NICU) is presented: mother, nurse and organization. By exploring these interconnected relationships and the emergent behaviors, a model of care that increases parental caregiving in the NICU is proposed. Supportive parent caregiving early in an infant's NICU stay has the potential for more sensitive caregiving and enhanced opportunities for attachment, perhaps positively impacting neurodevelopment.

Key words: NICU, Complex Adaptive System, Neurodevelopment, NICU Model of Care

A Framework of Complex Adaptive Systems: Parents As Partners in the NICU

In neonatal intensive care units (NICU) across the United States (US), preterm infants are surviving at earlier gestations and from more complicated clinical presentations than ever before.^{1,2} Beyond the success of their mere survival is the importance of providing a desirable long-term quality of life for these infants and their families.³ While evolving technology and practice have contributed to increased survival rates, mechanisms to lessen the impact of neurodevelopmental insults from traumatic early life experiences have not evolved at the same pace.^{4,5} The significance of this lack of progress in care delivery may be quantified in the degree of brain injury, presenting as somewhere along a continuum between *almost negligible to overt injury*. For the more ambiguous neurodevelopmental injury, sequelae may not be evident until long after neonatal intensive care. Thus the ability to make connections between a negative early life experience in the NICU and difficulties later in life may depend on a distant memory. Identifying evidence supporting the relationships between these events could provide avenues for changing routine practices in the NICU in favor of greater neuroprotection.

For decades scientists have demonstrated relationships between poorer neurodevelopmental outcomes and earlier gestational birth. Recently, however, a shift has occurred from predominantly motor deficits to recognizing a preponderance of cognitive, emotional and behavioral deficits.^{6,7} While research has demonstrated the detrimental effects of preterm birth on long-term neurodevelopmental outcomes, clinical practice changes supportive of brain health have been difficult to adopt.⁸ The challenges stem primarily from NICU systems issues and non-standardized approaches to the integration of developmental and family centered care.⁹⁻¹¹

This article proposes a NICU model of care that both acknowledges the highly complex and dynamic state of healthcare delivery today and, while working within those constraints, suggests a model that embraces active family participation. Integration of this model has the potential to improve neurodevelopmental infant outcomes while also increasing parent competence and satisfaction. Care in the NICU is multifaceted and not easily dissected into parts for examination; thus our discussion will use a Complex Adaptive System (CAS) framework, to provide greater understanding of the powerfully embedded, interconnected relationships of care and of how influential they are to infant outcomes. By using a CAS approach to describe and provide a deeper understanding the system of a NICU within the dynamic interplay of the agents most influential to infant outcomes, we can begin to build a NICU model of care best suited for the 21st century.

What is a Complex Adaptive System?

*The study of complexity... confronts us with the limits of human understanding.*¹²

Historically, scientists believed all things were capable of study through a linear and mechanistic method, able to be reduced to discrete parts. However as science evolved, complexity theory demonstrated that the universe is comprised of many types of complex interactive systems (e.g. the brain, immune systems, ecosystems, social and political systems). These complex systems cannot be understood in a traditional manner, because the systems and their sub-systems do not function in isolation. Rather they are dynamic and in perpetual concert with each other and their environment.¹³

Most environments and systems are not stagnant, as they typically need to adapt in order to survive and evolve. The concept of adaptability thus becomes the differentiating factor in a CAS framework versus a linear framework, namely the ability

to be dynamic and change as the result of stressors.¹⁴ Consequently, a complex adaptive system reflects the interaction between the various system parts and the environment, whereby distinctive behaviors emerge as the result of the system synergy and dynamism as seen in Table 1. The emergent behaviors are the effects of interactions, and occasionally of power struggles, within and between the system agents, as shown in Table 2 criteria for a CAS.¹⁵

A CAS is comprised of a network of agents that represent the various and diverse parts of a system.¹⁶ In a CAS there is no single locus of control, thus, agents act in parallel to one another. More importantly, the decisions or actions of each agent influence all the other related parts, resulting in an environment that is not fixed. Living organisms are commonly described in CAS frameworks; as such the uniqueness of each individual agent contributes to the concept of system unpredictability. Inherent in living organisms is the capacity for unique individual behaviors, based upon culture, values, genetics, history, and the like, to influence interactions. Furthermore, in complex systems involving people, it is our human uniqueness that denies outcomes to be controlled and predicted.

Within the healthcare setting agents often include patients, families, nurses, physicians, pharmacists, and others. Specifically within the NICU, the agents are routinely enmeshed to become a network supporting infant outcomes. The agents of focus in this article are parents, nurse and the organization, given the substantive contribution of each to infant outcomes. Importantly however, the functionality within and between the agents may be a factor of greater influence than is sometimes realized.

Through understanding the power of the interrelationships and examination of the behaviors, areas for change can be identified.

Why is the Phenomenon of Complex Adaptive Systems Important in the NICU?

Nearly 500,000 infants are born prematurely each year, and most require care in a NICU.^{17,18} While significant advances in medical management have resulted in decreased severity of persistent issues such as chronic lung disease and ophthalmic conditions, neurodevelopmental insults continue.¹⁹⁻²¹ Research has demonstrated that adverse behavioral, cognitive and emotional health outcomes plague many early born infants.²²⁻²⁴ Specifically, connections continue to be strengthened between preterm births and later social interactions, attention deficits, mental health issues and learning impairments. The exact cause of neurodevelopmental impairments has been difficult to identify because there are a host of inter-related factors that have the potential to contribute to neurodevelopmental vulnerabilities for high-risk infants, both within and beyond the NICU. Consequently, the issue of causality is a phenomenon of immense intricacy requiring greater attention if insults originating from post-birth medical care are to be teased-out and changes in the practice environment are to be considered.

Mental health impairments. Researchers have provided evidence of associations between anxiety, inattention, and social difficulties that manifest in a higher prevalence of autism spectrum disorders (ASD) and attention deficit/hyperactivity disorder (ADHD) for infants born preterm.²⁵⁻²⁸ This triad of behavioral disorders and symptoms has been suggested to represent a “preterm behavioral phenotype” that convey a general risk for all early born infants, with risk increased for those born earliest.^{29,30} Former preterm infants have also demonstrated higher incidences of depression and

anxiety than their full term counterparts.^{31,32} Even more interesting, young adults born small for gestational age have been found to suffer from depression requiring antidepressant therapies more often than peers.³³

Cognitive impairments. Additionally alarming is research related to preterm birth and cognitive deficits. In 2013, researchers demonstrated that a former preterm cohort performed significantly lower when compared with term peers on all cognitive and academic domains.⁶ Also, former early-born infants followed longitudinally showed a linear relationship between gestational age and cognitive ability; indicating that, as gestational age decreases, so does cognitive ability.³⁴ However, not all adverse preterm birth outcomes are experienced only by infants of the lowest gestational ages. Children born at 37-38 weeks, as compared with 39-40 week peers, had an increased risk for reading and spelling difficulties.³⁵

The research described above highlights adversity of a single organ, the human brain. Despite broad research conducted in various disciplines that highlight consequential neurodevelopmental outcomes in former preterm infants, we continue to see evidence that care in the NICU is not yet, brain-oriented to meet the health needs of this population.^{36,20,37-39} When considering the experiences that are unique to infants cared for in the NICU, as compared to full-term healthy infants, there are three distinctly abnormal early life experience: stress, pain and parental separation. While each of these experiences may be more profound for some premature infants than for others, the experiences are universal for all infants cared for in the NICU. Even more worrisome is that, when infants experience greater stress and pain (e.g. an infant is more ill or more unstable), they are more likely to experience greater separation from their parents

because nurses may act as more protective gatekeepers during this time. Additionally, parents may feel their presence and caregiving is less important when their infant is unstable and seemingly more in need of medical nursing care.

Chronic stress. As abnormal early life experiences, the three related but also individual factors of stress, pain and separation have been shown to exert significant negative effects on the developing brain.⁴⁰⁻⁴² When they represent a constellation of persistent experiences, this triad of experiences could be contributing to long term chronic stress, especially for infants residing in the NICU for extended periods of time. Of further concern, research has demonstrated that experiences of persistent chronic stress are most detrimental to the developing brain, sometimes even more so than a single severe insult.⁴³

Significant research links the deleterious effects from stress early in life on brain development. Moreover, when stress becomes chronic, alterations in the trajectory of brain development are possible, with further potential for hyperactive or exaggerated response to future stressors (evidenced in both animal and human models).^{44,45} Thus, the reactivity to chronic stress can be sensitized so that the response to subsequent stressors is substantially augmented; handling or events that might not have been stressful in isolation are stressful when coupled together, consistently or in tandem.⁴⁶ For example, a diaper change may seem to be a caregiving task of low stress; yet, when coupled with other caregiving task such as heel sticks, vital signs, and bathing, the diaper change may take the infant over the edge.

The chronic nature of the stress in the NICU with its varying degrees of intensity and little protection from repeated insults for infants, leave little doubt that the experience

may be traumatic for many infants.⁴⁷ In the NICU countless experiences of stress, pain and separation may be modifiable yet in practice many clinicians struggle to adhere to beneficial and permanent changes amid challenges within the system that provides competing demands.

Who Are the Agents in the NICU?

The agents described in this paper are both essential parts of the complex system, as well as those believed to exert the greatest influence on infants in the NICU. While seemingly simple individually, it is the complex relationships within and among them as individuals and the emergent power differentials that contribute to a greater whole of influence. The agents embedded within a patient care experience arrive to the exchange with their own history, culture and values. Furthermore, considering how this prior experience may affect subsequent relationships, a broad examination of each agent is presented here: parents, nurses and the organization.

Parents

During pregnancy most parents envision caring for their newborn after delivery. However, when an infant is admitted to the NICU, both the infant and the majority of his or her care are handed over to NICU nurses, leaving parents in a situation of little control. Often this experience can lead to parental feelings of inadequacy and promote barriers between themselves and the healthcare team.⁴⁸ When parental care is replaced by nursing care, a nurse-patient relationship is established between the nurse and infant. This relationship, although important to the infant's outcomes and even survival, may lead parents to question the meaningfulness of their involvement as a parent.

External to the NICU, parents are an agent within their own complex adaptive system. Upon entering the NICU, a parent becomes an agent of critical influence in the life of their infant. Acknowledging the life complexity of both parents, as well as the demands they juggle both permits and yet challenges NICU caregivers to offer optimal support.

When developing an effective inter-agent relationship with parents it is important to understand how each copes with having their infant in the NICU. Individual coping styles may be influenced by many factors. These factors may include the stress intensity of the current situation, general coping strategies and previous life experiences. For many parents, critical to their ability to cope is the state of their social support system at-large. A broad contextual understanding of the relationships in the life of each parent may assist nurses and other caregivers to offer meaningful support.

Nurses

Nurses are an integral part of any acute care organization because nurses both deliver and coordinate direct patient care. Bedside nurses are often the “gatekeeper” for the patient. Multiple disciplines rely upon the knowledge of the bedside nurse to provide care. In the NICU, each nurse functions as part of a network interconnected with physicians, nurse practitioners, physician assistants, patient care assistants, nutritionists, developmental therapists, social workers and several other hospital personnel and departments. It is well known that an infant cared for in the NICU for one month (the average length of stay in most NICUs is 21 days) may experience more than 100 care providers. Within this network, nurses negotiate patient care needs as fluctuations, limitations and changes occur to any element of the network. This same structure of

work extends beyond the walls of the NICU to the larger hospital organization. Thus, the work of a nurse is embedded within a complex and dynamic system reliant upon functional relationships to deliver optimal care.

The culture of any individual patient care department includes how professionals interrelate to and with one another. While a particular style or type of culture might be encouraged by a larger organizational standard, each individual department is subject to a particular culture of engagement dependent upon the individuals within a department. To further focus this discussion, nursing is one component of a larger organizational system, and nurses often have complex interrelationships within and among their peers that also impact their work. As can be said of any professional, the nurse's ability to deliver care and function within a greater network is influenced by multiple factors, including level of education, experience and personal values. These factors are embedded within the nurse's beliefs and values and interwoven within the fabric of individual nursing care, providing further evidence that the delivery of nursing practice is largely a heterogeneous entity. Thus, how individuals interact with each other and, in turn, how they interact with patients and families adds another layer of care delivery complexity. Navigating the uniqueness of each team member in the provision of care to a high-risk infant and their family lends itself to further exploration of the individual NICU in which care is provided.

Organization

The healthcare organization as a whole is another agent that influences the health of a patient. Individual organizations are themselves situated within the context of state and federal healthcare delivery regulations, as well as and deeply enmeshed within state

and federal political and financial systems. As a consequence, decisions made within the boardroom can have a direct effect on bedside care.

The purpose of a healthcare organization is to meet the health needs of the community it serves. While historically hospitals and other organizations have largely been self-determining, the rising costs of healthcare are creating financial crises that are in some cases resulting in organizational compromise.⁴⁹ As in any business model, economic profitability is essential. Despite the reality that hospitals are businesses, a societal perception exists that financial constraints should not be felt at the bedside, affecting safety or quality of care.⁵⁰

Soaring healthcare costs, decreasing reimbursement and fierce market competition are resulting in many organizations streamlining bedside care. In many cases this increases the demands placed on the direct patient care responsibilities of nursing.⁵¹ Nursing is not only responsible for providing highly skilled care, but also for supporting the business-type needs of patient care units: staffing, admission and discharge planning as well as patient flow coordination.⁵² Caregivers are distracted with competing unit-based responsibilities and thus are at high risk for making errors, resulting in less than ideal conditions for patients. Given the financial climate of healthcare today, for patients to be hospitalized they must meet strict severity of illness criteria. As a result, inpatients are acutely ill individuals. At the same time that nursing demands are increasing, patients are more vulnerable making quality nurse staffing a complex phenomenon. For NICU infants, whether or not the institution encourages bedside providers to provide optimal care may directly influence immature infants' neurodevelopment.

Current Model of Care

An important aspect of understanding how to improve neuroprotective care in the NICU may be to analyze how bedside care is provided. The overarching approach to care utilized by many pediatric facilities, both inpatient and outpatient, is family-centered care (FCC). The core principles that are the foundation of FCC are described in Table 3. While consensus has not been achieved on a single definition of FCC, agreement appears to exist that FCC represents a partnership between families and caregivers.^{10,53} This partnership ensures that the family is the cornerstone of support for a child and is well informed, supported and encouraged to participate in healthcare decision-making.

The model of care common to most NICUs is one in which nurses deliver the majority of hands-on care to high-risk infants with parents often treated as visitors in the environment and only “allowed” to participate in minor care delivery tasks. These tasks (e.g., diaper change, taking temperature and feeding) are often allowed once an infant becomes “stable”. Until the time stability has been achieved parents are more or less relegated to the sidelines and are observers in the care of their infant. Parents are often encouraged to provide touch and support to their infants yet, holding and cuddling (normal parenting strategies) are often limited by the caregiving environment of the NICU.

This model seems contrary to FCC’s philosophy.⁵⁴ While nurses certainly possess the technical skills and anticipatory critical thinking needed in an intensive care environment, this model complicates boundaries and may cause parents to question infant ownership. In the NICU, care delivery often places the nurse and infant together in a

partnership while parents are left on the periphery observing. The consequence of this unbalanced arrangement is that infants are often left in a situational void.

One aspect of the situational void results from infants being in the primary care of professionals whose job involves the care of multiple infants, lending to multiple competing responsibilities. An additional workplace reality is that nurses not only care for patients but also orchestrate the overall functioning of patient care units (staffing, admissions, discharges, patient flow), as described previously. In many cases this work may be accomplished in a less than ideal nurse-patient ratio⁵⁵. Thus healthcare professionals have many competing interests with the most acute need typically receiving the majority of the attention, whether patient or business needs.

In many NICUs the majority of parents are intermittently present, representing another aspect of the situational void. As mentioned previously, this void may be attributed to the unspoken, yet established, NICU boundaries. As a result, parents seem to be conditioned to believe their presence is not essential, rather that nurses are essential and parents are less necessary. Furthermore, because of the boundaries, many parents wait for staff permission prior to engaging with their infant. For many parents this results in a lack of comfort when responding to or handling their own baby. Unfortunately, for highly vulnerable infants this perpetuates the situational void because infants are thus at the mercy of both the healthcare professional and parental availability. This description is not a criticism, merely a reflection of the current model of care and the complex structure of many NICUs.

Future Model of Care

Gooding, Cooper and Blaine (2011) describe the philosophy of FCC and operationalize specific engagement activities for NICU families to participate in the care of their infants.¹⁰ The majority of suggested interventions consists of information sharing, collaborative decision making and support for each family as a unique entity. Despite the array of recommendations for parental involvement, however, the described FCC model stops short of suggesting that parents participate in direct caregiving while in the NICU. Consistent hands-on participation is not evident in many sources of information on FCC.^{9,53}

In contrast, Canadian researchers recently conducted an interventional NICU pilot study with 42 infants and mothers in which Family Integrated Care (FIC) was used as the care delivery model. For infants stable on continuous positive airway pressure (CPAP) or less respiratory support and receiving greater than 50% of feedings enterally, FIC necessitated a parent commit to spending at least 8 hours per day, five days each week as the infant's primary caregiver. For at least 3 weeks or until discharge, mothers attended daily rounds and received daily multidisciplinary educational sessions. During this time mothers provided infant care, as well as charting on their infants. Nurses retained responsibly for oversight of maternal care and technical aspects of care (e.g., nasogastric catheter insertion, CPAP prong placement, suctioning and oxygen management).⁵⁶

While this study had a number of limitations, including a lack of neurodevelopmental outcome data, its short-term outcomes assessed 21 days following intervention, indicated a statistically significant decreased incidence of stage 3 or greater retinopathy of prematurity and increased breastfeeding at discharge. A decrease was also

noted in parent stress at discharge. Interviews of participating parents demonstrated an increase in knowledge, confidence and enhanced relationships with clinicians; nurses reported closer relationships with parents.⁵⁶ To implement this model of care, nurses received broad education that allowed for enhanced understanding of the long-term importance of establishing the parent-infant relationship as early as possible. Ultimately this education refocused nursing care delivery to support the successful implementation of FIC.⁵⁷ A multi-site randomized control trial (RCT) is now underway in several NICUs in Canada that addresses many of the limitations of the pilot study.⁵⁸ The results of this RCT will provide greater insight into whether the results of this type of care are as effective as they seem.

In another developed country, interventions to increase parent participation have also been studied. Modeled from the humane neonatal care initiative, which focuses on the psychological needs of NICU infants, Sweden completed a RCT for infants who required level 2 care in which parental presence was necessary 24 hours a day and primary care for the infant was provided by the parents.⁵⁹ The results demonstrated that family care may decrease total length of stay and potentially chronic lung disease.⁵⁹

In the United States an RCT provided an educational-behavioral intervention aimed at improving child developmental and behavioral outcomes through supporting parent-infant interaction and parent mental health outcomes.⁶⁰

Culturally in the NICU, clinicians have come to believe that few others, especially parents, are able to deliver the expert care needed by patients. While nurses implement some tasks that parents should never have to perform on their own infant, the assumption must be that parents are responsible individuals who can and want to learn how to care

for their baby.^{61,62} Ultimately, parents who are taught to comprehensively assess their infant while in the NICU come to “know” their infant.⁶² Furthermore, nurses are the caregivers best suited to facilitate this education. This does not in any way diminish nursing’s importance in the care delivery process; rather, it supports the role of nurses to be stronger parent educators and evaluators of infant response.⁶¹ In doing so, this model equalizes the power and control distribution between parents and clinicians, whereby placing infants centrally to benefit from the relational support they need to develop appropriately from an emotional and cognitive perspective (see Figure 1).

As NICU providers we must demystify our healthcare knowledge and loosen the reins of what we consider allowable interventions for parents to provide. From a physiological systems viewpoint, presented in Table 4 are a few suggestions for how parental caregiving may be incorporated into clinical practice. To provide this caregiving, clinicians need to understand the strengths and limitations of each parent’s knowledge of the human body’s functioning; thus a baseline assessment will be necessary to guide the education and skill development.

In the FIC pilot study previously described, the intervention began when infants were “stable”.⁵⁶ While stability may be a reasonable starting point for FIC, it should not be our ultimate goal. Permissive parent-delivered care should be encouraged throughout the spectrum of care in the NICU; parent participation must be the practice norm from admission until discharge.⁶² In doing so we acknowledge the importance of parental support and comfort during times of both acute illness and recovery.

Active parent participation is crucial for both infants and parents because it decreases parent-infant separation and increases parent confidence.⁶³ Researchers have

demonstrated that active participation allows parents to gain competence in caring for their infant and facilitates sensitivity to infant cues.⁶⁴ For vulnerable infants, parent delivered care has the potential for both much stronger continuity of care once the infant is discharged from the NICU and transitions into community based care, as well as the opportunity to facilitate stronger attachment with their parent.

Conclusion

The NICU is a dynamic environment, with the dynamism largely due to the complexities of health and the human agent, as well as the current healthcare delivery challenges. Framing our encounters with the agents most influential to the health of an infant allows for sensitivity to the unique humanness of each agent and to the contribution each brings to a relationship. Using this lens allows for heightened awareness of how parents may approach their parenting role within and outside of the NICU, as well as how healthcare providers approach their work. From this broader vantage point, evaluating the NICU from a systems perspective encourages an objective analysis of practice with consideration for how each agent of care may unwittingly contribute to environments that are less than ideal for patients. The true focus of a redesigned model of care for the NICU necessitates evaluation of increased and earlier inclusion of agents most influential to vulnerable patients, in order to ensure that caregivers with long-term connections to patients are fundamentally involved in the delivery of care.

An opportunity to offer enhanced neurodevelopment support in the NICU may be for parents to provide the majority of direct care to their infant, with nursing focused on managing and monitoring technology, as well as the education, support and evaluation of

parent delivered care. The advantages may include decreased parent-infant separation and increased sensitivity to the pain and stress experiences of an infant. In totality, this caregiving approach may enhance an infant's neurodevelopmental trajectory.

Historically, the culture of care delivery in the NICU has rarely been questioned. Moving forward, the brain health of patients demand that clinicians question the manner in which care is delivered.

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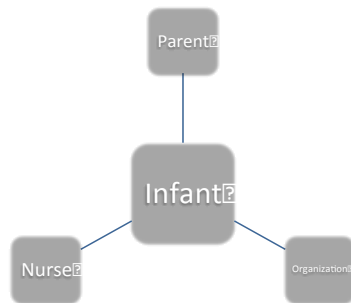
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Figure 1. Complexity hidden within the relationships that make up care in the NICU.

Old Model



New Model

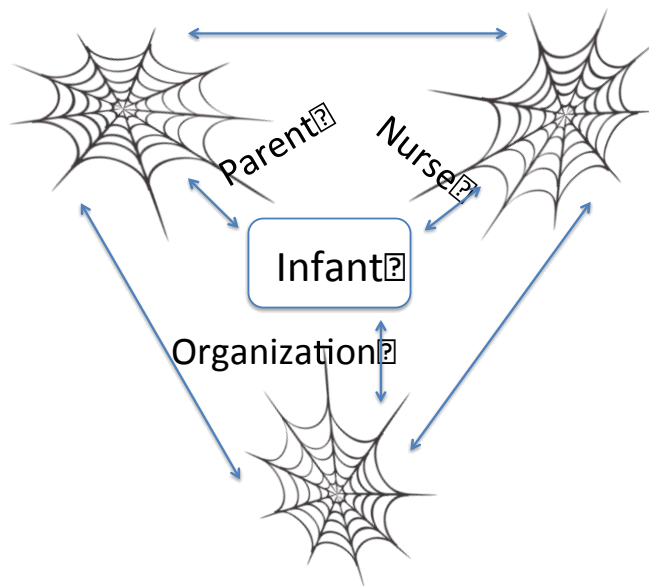


Table 1- Definition of Complex Adaptive Systems.

Complex-	many working parts connected in some way
Adaptive-	constantly changing
System-	set of elements that operate in relation to one another

Table 2- Criteria of a Complex Adaptive System (modified from Cilliers, 1998)

<ul style="list-style-type: none">-Large number of interactive elements-Interactions are rich, non-linear and in close proximity-Feedback loops present within interactions-Open systems; interact with their environment-Constant flow of dynamic energy-History influences present behavior
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Table 3- Core Principles of Family Centered Care (modified from AAP, 2003).

- | |
|---|
| <ol style="list-style-type: none">1. Respect each child and family2. Honor racial, ethnic, cultural, and socioeconomic diversity3. Recognize and build upon strengths of each child and family4. Support and facilitate choices about approaches to care and support5. Ensure organizational flexibility so services can be tailored to each child and family6. Share honest and unbiased information with families7. Provide formal and informal support for the child and family pregnancy through young adulthood8. Collaborate with families at all levels of health care9. Empower each child and family strengths, confidence, choices and decisions about their health |
|---|

Table 4. Examples of Parent Skill Development.

Respiratory	<ul style="list-style-type: none">• Assessment of general respiratory status (e.g. work of breathing)• Oral suctioning and mouth care• Skin assessment under and around respiratory equipment (nasal CPAP, endotracheal tube, etc)• Proper positioning of CPAP and cannula prongs
Cardiovascular	<ul style="list-style-type: none">• Color assessment• Obtain blood pressure• Assessment of normal heart rate for their infant
Fluid, Electrolytes and Nutrition	<ul style="list-style-type: none">• Assessment of dressing and integrity of access devices• Abdominal assessment• Stool and urine quality and quantity
Infection	<ul style="list-style-type: none">• Temperature regulation
Neurologic and Pain	<ul style="list-style-type: none">• Normal behavior and activity appropriate to developmental age• Neuroprotective strategies (e.g. light, noise, pain, stress)• Provision of consistent and extended skin to skin care
Skin	<ul style="list-style-type: none">• Skin integrity and overall evaluation
Other	<ul style="list-style-type: none">• Obtain daily weight

CHAPTER 4

FKBP5 Genotype and Early Life Stress Exposure Predict Neurobehavioral Outcomes for Preterm Infants

FKBP5 Genotype and Early Life Stress Exposure Predict Neurobehavioral Outcomes for Preterm Infants

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Abstract

Problem: While prematurity is the greatest risk factor, both genetics and environment serve as contributing risk factors for health trajectories for infants spending extended lengths of stay in the neonatal intensive care unit (NICU). The purpose of this study was to explore the relationship between stressful early life NICU experiences, genetic variation of a stress response-associated gene (FKBP5) and neurobehavioral outcomes.

Method: We examined genetic variation in relationship to stress experience for effects on neurobehavioral outcomes in a total of 41 preterm infants. Buccal swabs were collected for genotyping of FKBP5 SNPs. Exploratory data analysis was used to obtain initial insights into the effects of FKBP5 genotype, NICU stress experience, and their interaction on infant neurobehavioral development at 35 weeks post-menstrual age.

Results: A significant gene x environment interaction was observed in stress exposure from NICU care and genotype of FBKP5 on several neurobehavioral scores. Also 2 main effects from stress and genotype were identified using NISS Total Average Stress score to predict poorer neurobehavioral assessments. The sample size limits generalizability of these results.

Implications: Evidence of genetic and environmental risk factors for neurodevelopmental impairment suggests the need for improved evidence-based practice initiatives to protect those that are most vulnerable due to the combination of genetic susceptibility to stress and medical fragility. Evidence from this study highlights the need for enhanced neuro-protective and stress reduction protocols in the NICU.

FKBP5 Genotype and Early Life Stress Exposure Predict Neurobehavioral Outcomes for Preterm Infants

Background

Early life experiences are considered the developmental underpinning of physical and emotional health (Als et al., 2004; Bowlby 2005; McGowan & Szyf, 2010). Accumulating literature provides evidence supporting linkages between early life experiences and lifelong health and illness (Fox et al, 2010; McGowan & Szyf, 2010; Gudsruk & Champagne, 2011). For infants requiring admission to the neonatal intensive care unit (NICU), early life experience is particularly significant (Xiong & Gonzalez, 2012). The NICU is focused, first and foremost, on life saving measures but the complex trauma experienced during care may have both acute and long-term impact on health and developmental functioning. A vulnerable infant in the NICU encounters many more insults than the average person requiring acute hospitalization. For example, these infants experience disruption in parental relationships, repeated stressful experiences and pain that is often underappreciated and/or undertreated. Many of these treatment-related experiences fit the classic definition of “uncontrollable stress exposure”, a circumstance that has known deleterious effects on physical, cognitive and socioemotional health (Joels & Baram, 2009; McGowan et al., 2009).

While stress can have beneficial effects for growth and development, the intensity and chronicity of stress can overburden an individual leading to detrimental effects. Acute stress response encourages behavioral adaptation to a challenge and mobilizes the metabolic resources to make that adaptation possible. However, chronic stress can be even more destructive and has been shown to negatively impact brain structure (Joels & Baram, 2009; Pineda et al., 2014). The physical response to stress is characterized by the

release of stress mediators as a result of sympathetic nervous system (SNS) activation and hypothalamic-pituitary-adrenal (HPA) axis, respectively. Following stress exposure, the physiological response to stress is resolved via a negative feedback loop. If there is dysfunction in this process, the stress response continues unchecked. The deleterious effects of chronic stress have been preferentially attributed to prolonged exposure to glucocorticoids (Lucassen et al., 2014). Yet the pathway from the release of glucocorticoids to physiological effect is complex and individual differences in sensitivity to those stress signals may also play a role in determining when these processes transition from adaptive to maladaptive.

The stress response is a multifactorial trait influenced by genetics and the environment. Individual differences in this response are likely the result of variation within multiple genes, including those encoding the physiological aspects of stress responding as well as the psychosocial response to stress exposure. The candidate gene *FKBP5* has been selected for this research because of its recent identification as an important HPA functional regulator of the glucocorticoid-mediated stress response. *FKBP5* is located on chromosome 6 and encodes FKBP5, the FK506 binding protein 5, which plays an important role in immunoregulation as well as protein folding and trafficking. Activation of glucocorticoid receptors by cortisol results in the synthesis of FKBP5, which subsequently decreases glucocorticoid receptor sensitivity for cortisol binding. As a result, FKBP5 is a powerful regulatory mechanism involved in the physiological resolution of stress effects. Single nucleotide polymorphisms (SNP) in the *FKBP5* are associated with differences in glucocorticoid receptor sensitivity and stress hormone system regulation. Four SNPs have been selected for inclusion in this study as

they have been previously associated with variation in the impact of stressful life experiences on mental health factors, rs1360780, rs3800373, rs9296158, rs9470080 (Binder et al., 2008; Klegel et al., 2013). The minor allele at each of these SNP locations is present in 20-30% of the population, making it fairly common in the general population.

Alleles associated with HPA axis dysregulation have also been identified as a risk factor for stress-related psychiatric disorders (Binder et al., 2004; Holz et al., 2014), including post-traumatic stress disorder (Klegel et al., 2013). Because of the way PTSD is defined in terms of mental health, it has not been considered a valid diagnostic phenomenon in the infant population. Given the parallels between the NICU experience and more traditional scenarios where PTSD develops, particularly those characterized by intense and/or chronic stressful experiences, we hypothesize that the FKBP5 gene may play a role in conveying risk and/or susceptibility to the medical trauma associated with the NICU experience.

Significant individual variability in the response to preterm birth and NICU stay has been noted in both research and clinical settings. Many infants exposed to the stressful early life experience of the NICU show normal neurodevelopmental status and reach milestones as expected. As such, it is unlikely that the impact of the NICU environmental is entirely responsible for the negative outcomes reported. As with many outcomes of complex etiology, it is the interaction of innate (genetic) and environmental factors that shapes the long-term developmental course. Given the regulatory role of FKBP5 in the stress response, we hypothesize that polymorphisms within this candidate gene will modulate the effects of stress experienced by preterm infants in the NICU

(Mehta et al., 2011; Bevilacqua et al., 2012). Exploration of this candidate gene and the NICU environmental exposure could offer insight into the gene x environment interaction. The purposes of this study were: (1) to explore the relationships between FKBP5 SNPs and neurodevelopment; and (2) explore whether an interaction occurs between FKBP5 SNPs and stress experiences.

Methods

Design

A prospective observational design was used to conduct the study.

Sample

A cohort of preterm infants admitted to Connecticut Children's Medical Center NICUs, one located in Hartford and the other in Farmington, CT, were invited to participate in this study. We received family consent for the inclusion of 45 infants born at 26 - 32 6/7 weeks GA, from October 2014 until September 2015. The final total of 41 infants was based on the inclusion of only those infants with completed neurobehavioral assessments (NNNS). During this time period, 50 infants were eligible to participate. Five parents declined to consent to the study, with the most cited reason for decline being the potential for additional infant stress as a result of the neurobehavioral examination. Infants were excluded if they had: (1) chromosomal or genetic anomalies; (2) significant central nervous system abnormalities, including grade III/IV intraventricular hemorrhage; (3) been born to a mother with a history of substance abuse during current pregnancy, and (4) mother younger than 18 years of age. The Institutional Review Board at Connecticut Children's Medical Center, Hartford, CT, approved this study. Informed parent consent was obtained before enrollment in the study.

Procedures

After enrollment, infants were sampled once for DNA during their study participation. Data related to the infant stress and pain experience were collected from the electronic medical record for the first 21 days of NICU care. Infants were examined once using the NICU Network Neurobehavioral Scale (NNNS); a neurobehavioral assessment prior to discharge.

Genotyping

DNA was extracted from buccal epithelial tissue using a soft cotton swab and standard protocols (Qiagen, Gentra® Puregene® Buccal Cell Kit, #158845). All samples (N=41) were genotyped for 4 SNPs of *FKBP5* (rs3800373, rs9296158, rs1360780, rs9470080) using predesigned TaqMan primers and universal genotyping master mix (Life Technologies, C_27489960_10, C___1256775_10, C___8852038_10, C___92160_10). Genotyping assays were performed according to manufacturer protocol using an Applied Biosystems Step One Plus PCR machine and ABI allelic discrimination software.

Demographic data

Maternal and infant demographic data were collected. Maternal data included: age, pregnancy history and complications and race. Infant data included: gestational age, gender, race, birth weight and length, mode of delivery, apgar scores, resuscitation at delivery, SNAPPE II score (degree of illness) and length of stay.

Instruments

SNAPPE-II

The SNAPPE-II is an illness severity score used as a predictor of mortality (Richardson et al., 2001; Dammann et al., 2010). This measurement characterizes infant mortality within the first 12 hours of life; it is not designed to be used as a cumulative measurement. Data collected for this instrument include physiologic variables, birth weight, and apgar scores. This data can be collected retrospectively from the infant's medical record. In this study SNAPPE-II scores were used to provide a baseline measure of infant severity of illness.

Neonatal Infant Stress Scale (NISS)

The NISS is a ranked quantitative instrument used to collect information concerning daily stress experiences of infants during care in the NICU (Newnham et al., 2009; Smith et al., 2011). Common NICU interventions are ranked on a 5-point scale as not stressful, a little stressful, moderately stressful, very stressful and extremely stressful. The data can be collected retrospectively from the infant's medical record. The NISS scale was originally developed in Australia; the instrument language has been modified to meet clinical care terminology for United States clinical care. Each attempt at a procedure was counted as one stress event. The weighted NISS data is collected daily, resulting in a totaled daily score that measures daily stress. In this study, the daily total scores were used both as a daily stress variable and as a cumulative stress variable (cumulative daily scores).

NICU Network Neurobehavioral Scale (NNNS)

The NNNS is a standardized assessment of neurobehavioral functioning of the high-risk infant, including neurologic, behavioral and stress signs (Lester et al., 2004; Liu et al., 2010). The three main sections are neurologic items for tone and reflexes;

behavioral items of state, sensory, and interactive processes; and stress/abstinence. The NNNS yield 13 summary scores; with higher scores indicating better function see Table 1 for brief description. A reasonable age range for use of the exam is 34-48 weeks (corrected age). Examination of neurobehavioral functioning was planned for after 35 weeks post menstrual age (PMA), allowing for a standardized approach for neurobehavioral comparison.

Table 1. NNNS Summary Score Components.

Habituation	Response decrement to repeated auditory and visual stimuli
Attention	Response to animate and inanimate auditory and visual stimuli
Arousal	Level of arousal including state and motor activity during exam
Regulation	Capacity to organize motor activity, physiology & state during exam and response to cuddling, consoling and negative stimuli
Handling	Handling strategies used during orientation to maintain alert state
Quality of movement	Measure of motor control including smoothness, maturity, lack of startles and tremors
Excitability	Measure of high levels of motor, state & physiological reactivity
Lethargy	Measure of low levels of motor, state & physiological reactivity
Asymmetric reflexes	Any asymmetric response to reflex elicitation
Nonoptimal reflexes	Any non-optimal response to reflex elicitation
Hypertonicity	Hypertonic response in arms, legs, trunk or in general tone
Hypotonicity	Hypotonic response in arms, legs, trunk or in general tone
Stress/abstinence	Amount of stress and abstinence signs observed during exam
· Physiological	· Breathing pattern & work of breathing
· Autonomic	· Sweating, spit-up, hiccoughing, sneezing, nasal stuffiness and yawning
· CNS	· Abnormal suck, tremors, startles, hypertonia, back arching, etc.
· GI	· Gagging/choking, loose/watery stool, excessive gas and bowel sounds
· State	· Cry, extreme irritability, abrupt state change, lack of quiet awake, etc.
· Skin	· Pallor, mottling and cyanosis
· Visual	· Gaze aversion, visual locking, hyperalertness, roving eyes, etc.

Statistical Analysis

Descriptive statistics were conducted to analyze sample demographic data. Linear regression analysis was used to explore the relationship between the candidate gene SNPs and neurobehavioral outcomes, with each NNNS summary score as the dependent variable. In the first step we entered biological predictors influential to health outcomes (e.g. gestational age, gender, birth weight and race). The second step of the model included the Total Average Stress score for each infant. The final step of the regression model included the genotype of each SNP, see results in Table 6. Additionally, analyses examined the gene interaction effects with total average NISS data.

Results

Participant Characteristics of Final Data Set

The majority of infants were identified as white and non-Hispanic. All infants were <33 weeks gestation, with a mean gestational age of 30.1 (\pm 2.2) weeks PMA. The proportion of males compared to females was 53.7%, and the majority of infants were delivered via caesarean section birth. The mean age of mothers was 33 (\pm 5.5) years. Infants received NNNS examination at a median age of 36.2 weeks PMA (36.4-39.4). Infant and maternal demographic data are presented in Table 1. The Total Average Stress was 128 (\pm 28). While the majority of infants did not have a diagnosed intraventricular hemorrhage (IVH) on neonatal ultrasound, 10% did have grade 1 or grade 2 IVH following a repeat ultrasound.

Table 2. Sample Characteristics.

Infant:	
• Gestational age at birth, weeks	30.1 (\pm 2.2)
• Gender, % males	53.7
• Birth weight, grams	1317 (\pm 488)
• Race, %	
○ White	68
○ Other	20
○ Black	12
• Hispanic, % no	95
• Mode of Delivery, % c-section	78
• SNAPPE-II	15 (1 \pm 4)
• Total Average Stress	128 (\pm 28)
• Cranial ultrasound, %	
○ 1 st - N/A, Neg., Grade 1 or 2	37, 58, 5
○ 2 nd - N/A, Neg., Grade 1 or 2	61, 29, 10
○ 3 rd - N/A, Grade 1 or 2	93, 7
• Length of stay, days	56 (\pm 30)
Mother:	
• Age	33 (\pm 5.5)
• Marital Status, % married	56

N= 41; *Values are mean (SD)

Stress Exposure in the NICU

Descriptive NISS Data

Stress data is presented first in this analysis, as NICU stress exposure appears to be significantly associated with neurobehavioral outcomes. To begin, the intensity and chronicity of exposure to stress from birth to 21 days of life in the NICU was explored. Each infant's daily encounter of stressful procedures, which include extremely stressful, very stressful, moderately stressful and a little stressful, were tallied to understand the frequency and various intensities of procedures infants endure in the NICU. The data were collected in two ways, 1) daily counts of each stress category were completed,

allowing for an understanding of how many times infants are subjected to each type of stressor, and 2) using the weighted scores for categories of NISS stress, a total daily stress score was calculated for each day of data collection. These data are presented in two figures. Shown in **Figure 1** is the percentage distribution for the counts of daily stress experiences. Given the lesser frequency of extremely stressful procedures, extremely and very stressful measures were combined into a single category. The 21-day cumulative daily scores of stress are presented in a line graph, **Figure 2**. Additionally, the total daily stress scores were averaged over 21-days, allowing for a Total Average Stress Score. The Total Average Stress score was used in several data analysis.

Figure 1. Percentage of stress type over 21 days in NICU.

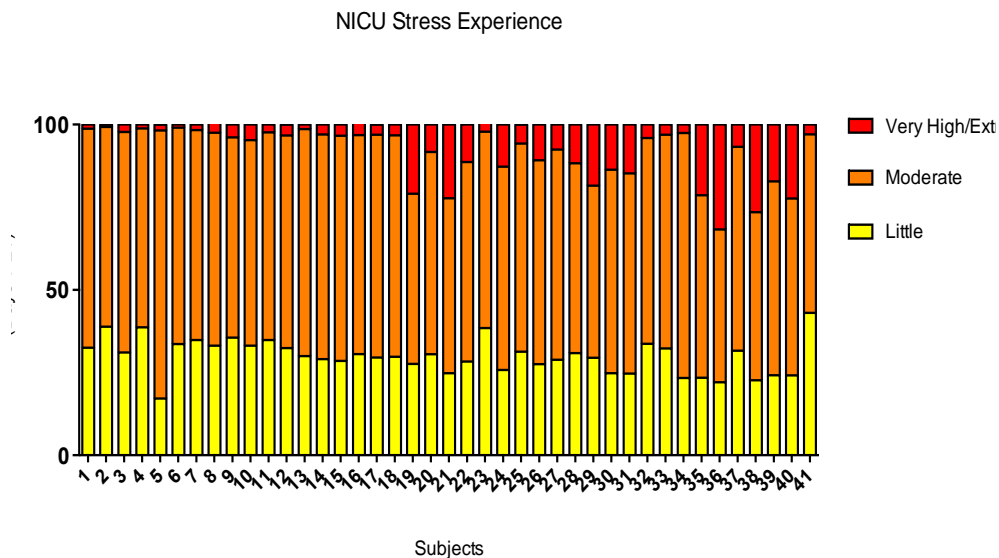
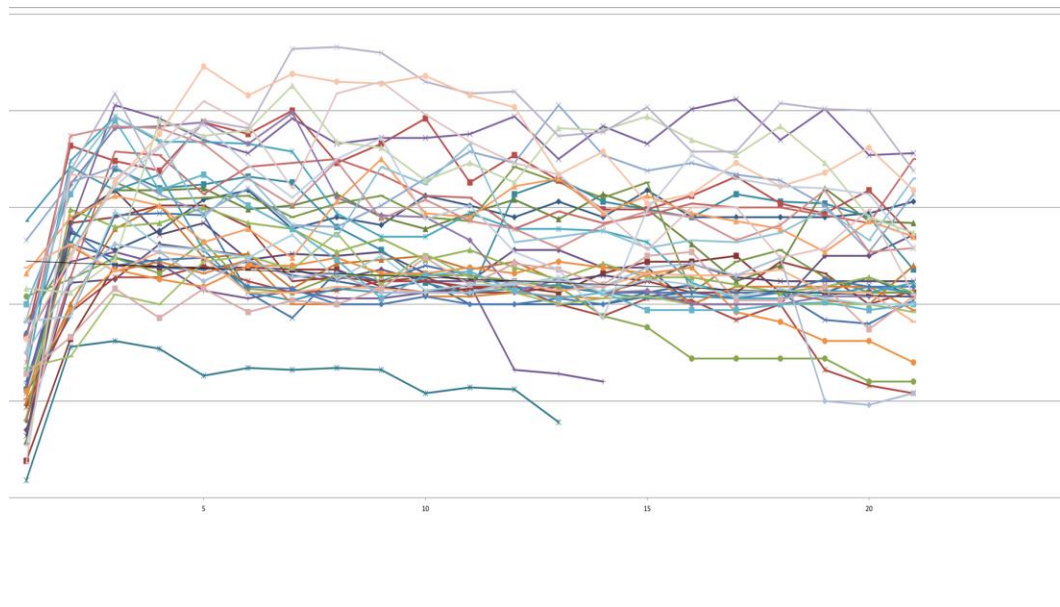


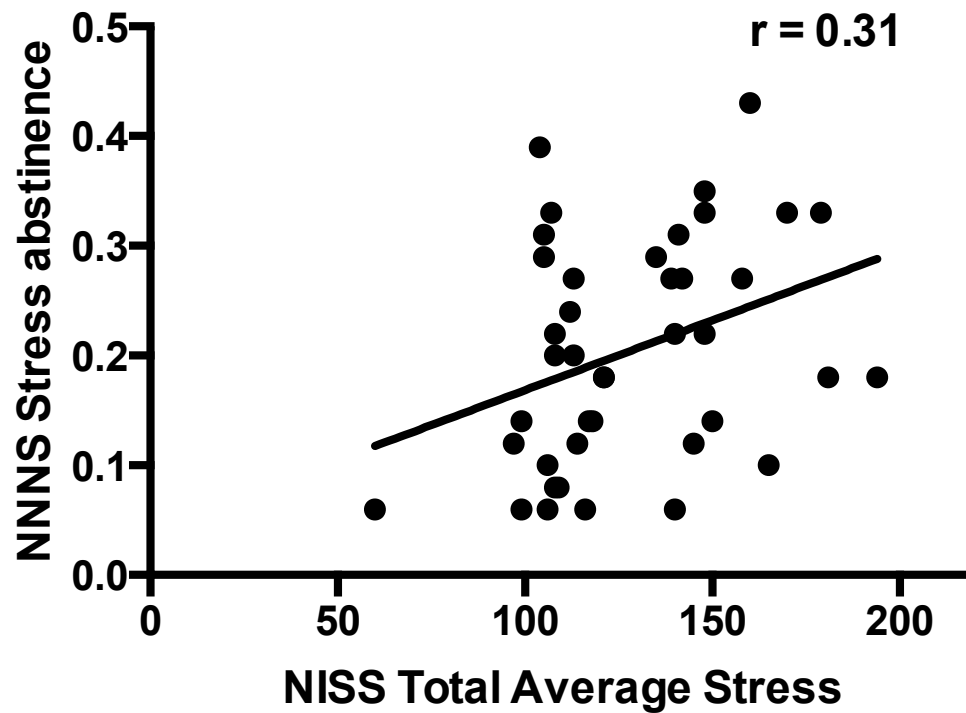
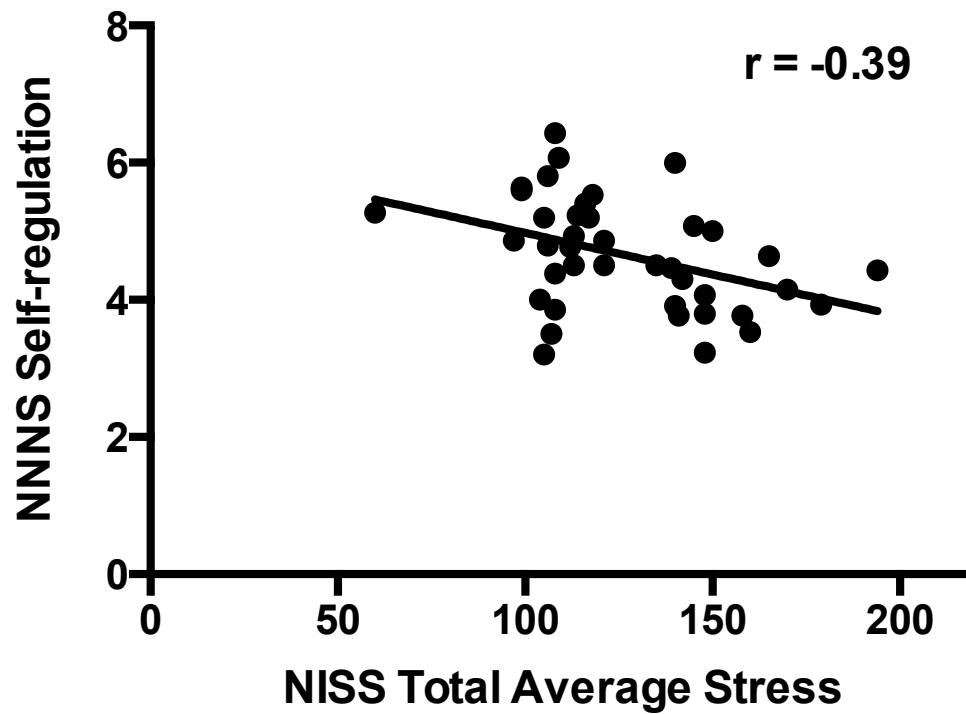
Figure 2. Total daily stress over 21 days in the NICU.

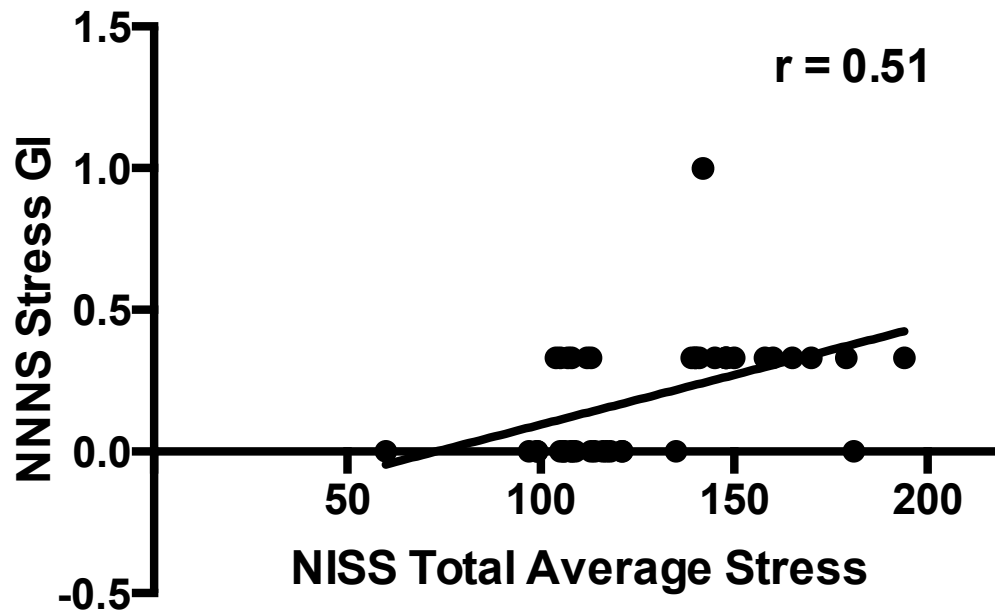


Stress and NNNS Neurodevelopment

Using Spearman correlation to decrease the effects from outlier data, we investigated the relationship between an infant's Total Average Stress experience and NNNS neurobehavioral outcomes. This is an analysis not originally planned, however became of interest as the study progresses. Statistically significant results were identified for the following summary scores: Self-Regulation, Stress-Physiological, and Stress-GI. A moderate correlation was seen with Stress Abstinence, see Table 4. The NNNS summary score components are presented in Table 5.

Figure 3. NISS Total Average Stress Correlation with NNNS, both figures indicate as Total Average Stress increases the neurobehavioral indication increases.





Genetic Variation

Genotype Correlations

Next, all infants were genotyped for *FKBP5* SNPs rs3800373, rs9296158, rs1360780 and rs9470080, with respective minor allele frequencies of 0.46, 0.46, 0.49 and 0.51. These frequencies are slightly higher than HapMap data, CEU population as a reference (the known HapMap allele frequencies for rs3800373, rs9296158, rs1360780 rs9470080 are: 0.24, 0.27, 0.27 and 0.30), however all genotype frequencies were in Hardy-Weinberg equilibrium. To verify accuracy and call rate, 17% of the samples were duplicated, yielding 100% reproducibility. Due to the small sample size, recessive alleles were combined and genotype frequencies were compared using the following model: rs3800373 AC + CC and AA (18, 23); rs9296158 AG + GG and AA (18, 23); rs1360780 CT + TT and AA (19, 22); rs9470080 CT + TT and CC (21, 20). Shown in Table 2 is the genotype frequency for each SNP.

Table 3. FKBP5 Genotype Frequencies. *MAF denotes minor allele frequency.

Genotype	Nucleotide variation	Genotype counts	MAF*
SNP 1- rs3800373	A/C	AA AC CC	
		23 17 1	19/41= 0.46
SNP 2- rs9296158	A/G	AA AC CC	
		23 17 1	19/41= 0.46
SNP 3- rs1360780	C/T	CC CT TT	
		22 18 1	20/41= 0.49
SNP 4- rs9470080	C/T	CC CT TT	
		20 19 2	21/41= 0.51

A correlation analysis of FKBP5 genotype identified significant linkage disequilibrium among SNPs rs3800373 and rs9296158, with rs1360780 and rs9470080 having more moderate correlations, see Table 4. The 100% linkage disequilibrium of rs3800373 and rs9296158 allowed for analysis of only one of the SNPs, rs3800373 was randomly selected as the tagging polymorphism.

Table 4. FKBP5 SNP correlations.

	SNP 1	SNP 2	SNP 3	SNP 4
SNP 1- rs3800373		1.000**	.955**	.822**
SNP 2- rs9296158	1.000**		.955**	.822**
SNP 3- rs1360780	.955**	.955**		.860**
SNP 4- rs9470080	.822**	.822**	.860**	

Sample size, N=41; **Significance < .05

FKBP5 Genotype and Neurobehavioral Assessment

The correlation of Total Average Stress and NNNS outcomes were examined, the statistically significant and moderately significant findings are presented in Table 5.

When controlling for biological and stress factors, the regression analyses between FKBP5 SNPs and neurobehavioral assessment revealed genotype to be a predictor for Excitability and Stress State summary scores, see Table 6 and Figure 4. Stress State is a component of the overall NNNS Stress/Abstinence Summary score.

Table 5. Significant Correlations for Total Average Stress and NNNS Summary Scores.

	NNNS Self Regulation	NNNS Stress Physiological	NNNS Stress GI	NNNS Stress Abstinence	NNNS Lethargy
Total average stress	-.393*	.314*	.511**	0.307	0.287
	0.012	0.046	0.001	0.051	0.069

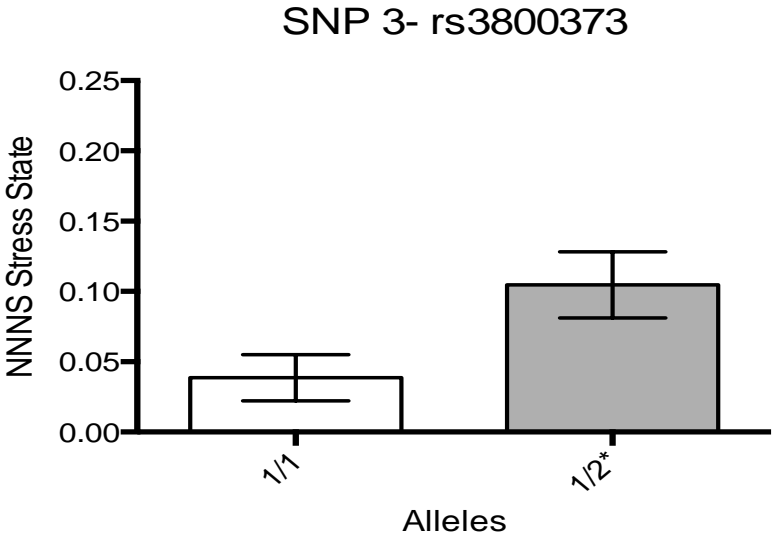
Table 6. Regression model NNNS Excitability, Total Average Stress and Genotype. Controlling for biologic factors and stress indicates a main effect of genotype.

Excitability Summary Score						
Tested FKBP5 SNP						
	rs1360780			rs9470080		
	<i>F-change</i>	<i>R²-change</i>	<i>p-value</i>	<i>F-change</i>	<i>R²-change</i>	<i>p-value</i>
Model 1- Race, GA, gender, birth weight	0.145	0.169	0.145	0.145	0.169	0.145
Model 1 + Total Average Stress	0.871	0.001	0.238	0.871	0.001	0.238
Model 2 + genotype	0.021	0.122	0.055	0.002	0.2	0.011

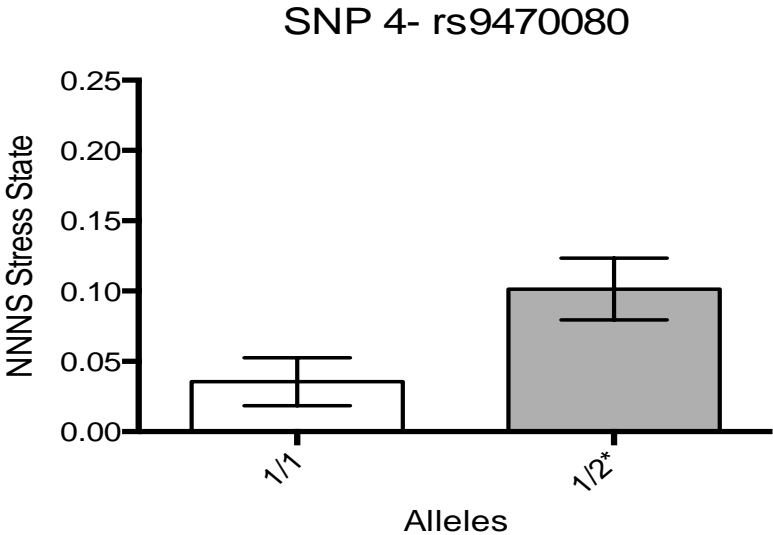
Table 7. Regression model NNNS Stress State, Total Average Stress and Genotype. Controlling for biologic factors and stress indicates a main effect of genotype.

Stress State Summary Score						
Tested FKBP5 SNP						
	rs1360780			rs9470080		
	<i>F-change</i>	<i>R²-change</i>	<i>p-value</i>	<i>F-change</i>	<i>R²-change</i>	<i>p-value</i>
Model 1- Race, GA, gender, birth weight	0.059	0.218	0.059	0.059	0.218	0.059
Model 1 + Total Average Stress	0.058	0.077	0.026	0.058	0.077	0.026
Model 2 + genotype	0.048	0.077	0.01	0.032	0.09	0.008

Figure 5. Differences in NNNS Stress score by FKBP5 genotype at SNPs rs1360780 and rs9470080. Individuals with copies of risk allele have increased summary scores.

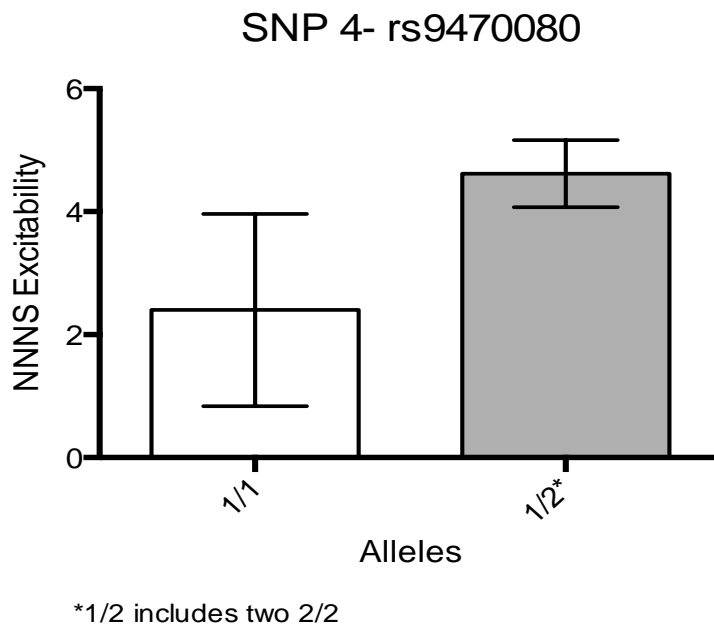
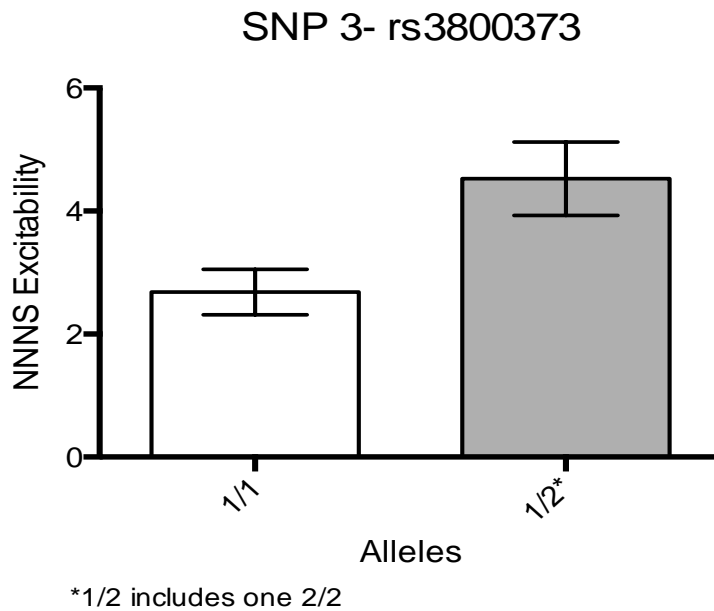


*1/2 includes one 2/2



*1/2 includes two 2/2

Figure 6. Differences in NNNS Excitability score by FBPB5 genotype at SNPs rs1360780 and rs9470080. Individuals with copies of risk allele have increased summary scores.



Gene x Environment Interaction

The gene x environment interactions were analyzed by multivariable linear regression using analysis of covariance approach. Each NNNS Summary Scores (continuous variable) was individually included as the dependent variable with Total Average Stress (continuous variable) and genotype (categorical variable) at each SNP location as independent variables. See Table 8 for significance results and Figure 7 for interaction findings.

Table 8. Gene x environment interactions, FKBP5 genotype & stress with NNNS.

	SNP 1- rs3800373	SNP3- rs1360780	SNP 4- rs9470080
Habituation	0.99	0.99	0.67
Attention	0.91	0.50	0.80
Arousal	0.79	0.70	0.58
Regulation	0.98	0.64	0.98
Handling	0.62	0.94	0.98
Quality of movement	0.27	0.08	0.22
Excitability	0.55	0.61	0.94
Lethargy	0.68	0.60	0.80
Asymmetric reflexes	0.22	0.27	0.70
Nonoptimal reflexes	0.01	0.02	0.00
Hypertonicity	0.28	0.35	0.96
Hypotonicity	0.24	0.19	0.76
Stress/abstinence	· 0.45	· 0.89	· 0.83
· Physiological	· 0.94	· 0.75	· 0.75
· Autonomic	· 0.01	· 0.04	· 0.16
· CNS	· 0.27	· 0.55	· 0.23
· GI	· 0.21	· 0.34	· 0.25
· Stress State	· 0.25	· 0.43	· 0.37
· Skin	· 0.53	· 0.69	· 0.86
· Visual	· 0.76	· 0.84	· 0.92

Figure 7. Interaction of NISS Total Average Stress and FKBP5 genotype (rs3800373) on NNNS Nonoptimal Reflex ($p>0.01$) and Stress Autonomic scores ($p>0.01$).

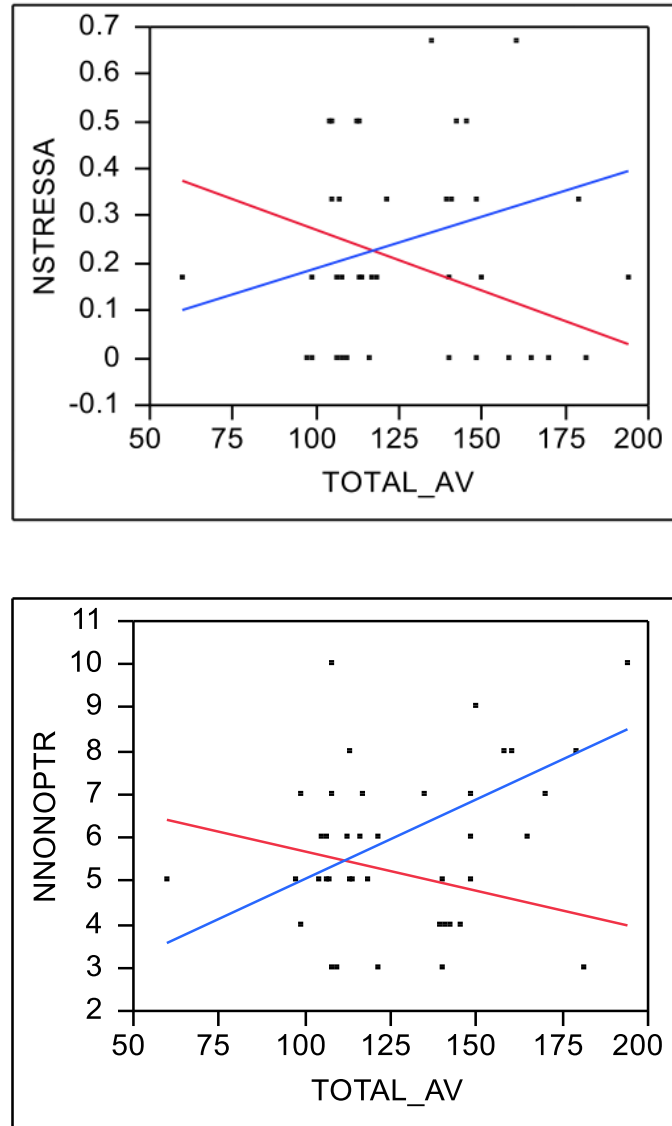


Table 10. 2x2 table of genotype and stress exposure for NNNS Nonoptimal Reflexes with *FKBP5* rs3800373, rs1360780 and rs9470080.

	Low stress	High stress
1 or 2 copies of Risk allele*	Low scores	High scores
Protective allele	Moderate scores	Moderate scores

Table 11. 2x2 table of genotype and stress exposure for NNNS Stress Autonomic with *FKBP5* rs3800373 and rs1360780.

	Low stress	High stress
1 or 2 copies of Risk allele*	Low scores	High scores
Protective allele	Moderate scores	Moderate scores

Discussion

Infant outcomes following NICU stay vary widely between individuals though the factors contributing to these outcomes remains to be fully elucidated. The present findings suggest that environmental factors act synergistically with genetic susceptibility to affect neuro behavioral outcome. We analyzed the effects of stress exposure and genetic variation of *FKBP5*, a stress-associated gene, on neurodevelopmental outcomes. The primary finding observed 2 main effects, increased stress exposure in the NICU is associated with poorer neurobehavioral outcomes and having at least one copy of the *FKBP5* minor allele is also associated with poorer neurobehavioral outcomes in preterm NICU infants. Additionally, a significant gene x environment interaction was identified between stress and *FKBP5* genotype on neurodevelopmental outcomes.

To investigate the main effects of stress and genotype on neurodevelopmental outcomes, a correlation analysis of NISS Total Average Stress for NNNS Summary Scores was completed. Using Spearman's correlation we identified stress exposure to be associated with neurobehavioral health in several measurements: Self Regulation, Stress/Abstinence, Stress Physiological and Stress GI. Next, to examine the effect genotype has on NNNS Summary Score we performed general linear regression, controlling for biological and stress related confounders associated with prematurity and medical care. It was determined that polymorphism rs1360780 and rs9470080 were

associated with the NNNS Excitability and Stress State Scores. These analyses demonstrate that independently the factors of NICU stress exposure and genotype each influence an infant's state of neurodevelopmental health.

To further explore, an investigation was conducted on what occurs if these independent factors are combined, to do that an interaction analysis was conducted. By performing a multivariable linear regression using analysis of covariance, NNNS Summary Score as the dependent variable and Total Average Stress and genotype as independent variables, an interaction was observed. For the Summary Scores of Nonoptimal Reflexes, those with at least one copy of the risk allele, when in a low stress environment infants have more optimal reflexes. However, when these infants have high stress exposure, they have sharply higher scores for nonoptimal reflexes. This outcome was identified across all polymorphisms in this study. Additionally, the summary score of Stress Autonomic identified a similar pattern. For those infants with the risk allele and a high stress environment, there is evidence of increased autonomic stress response, see Table 9. Interestingly, when infants with the risk allele are in a low stress environment, they actually present with better neurobehavioral repertoire than those infants with the protective risk allele. This data mirrors that which is described in the literature (Bevilaqua, 2012). Considering the mechanism in which chronic stress results in detrimental outcomes, if polymorphisms within the FKBP5 gene, when exposed to increased stress, alter stress associated neural pathways, NICU infants with specific FKBP5 allele variants may be at higher risk for poorer neurodevelopment.

The influence of *FKBP5* genotype on brain health outcomes has been examined in limited populations. Binder et al. (2008) found that in adults who experienced childhood

abuse, SNPs of *FKBP5* were a predictor of adult post-traumatic stress disorder (PTSD). These results are similar to other findings of an interaction between *FKBP5* minor allele risk polymorphisms with childhood adversity to modify the risk for PTSD (Xie et al., 2010; Mehta et al., 2011).

In children who experienced an acute medical injury, *FKBP5* polymorphisms were associated with peritraumatic disassociation (Koenen et al., 2005). Interestingly, in study of 14-month-old infants and the quality of their parental attachment relationship, the minor allele of *FKBP5* rs1360780 demonstrated an additive effect with cortisol reactivity; higher cortisol reactivity was seen in infants with more risk alleles (Luijk et al., 2010). Also, an interaction was found between *FKBP5* and insecure-resistant attachment. This suggests a heightened risk for *FKBP5* minor allele carriers, with either 1 or 2 copies, who also have an insecure-attachment relationship with their mother (Luijk et al., 2010). Consistent with other studies, our work provides novel evidence of the risk for poorer neurodevelopmental outcomes in the preterm NICU infant population if infants are carriers of the *FKBP5* risk allele.

The NNNS assessment used to measure outcome, measures at-risk infant neurobehavioral organization, neurological reflexes, motor development, tone and stress (Lester et al., 2004). Specifically describing an infant's level of developmental and behavioral maturation, central nervous system integrity and stress response (Lester et al., 2004). The NNNS has been used to examine infant groups include: healthy full-term, preterm, and prenatally drug-exposed infants (Fink et al., 2012; Montirosso et al., 2012; Sucharew et al., 2012). Research has shown that when evaluated early in life, NNNS assessment predicts longer-term medical and behavioral outcomes (Liu et al., 2010; El-

Dib et al., 2012). This suggests the earlier infants are identified as at-risk, the earlier interventional support can begin. While factors that influence neurodevelopment are multifactorial, in this small sample, significant relationships were found between degree of stress exposure and outcomes, which is consistent with other findings (Montirosso et al., 2012).

The NISS stress data collected from the infants in this sample demonstrate that while a lesser percentage of infants in the NICU endure overwhelming amounts of cumulative high stress, all infants experienced remarkable amounts of moderate and low stress, **Figure 1**. An interesting observation exists in the temporal line graph of total daily stress experiences, **Figure 2**. First, the infants appear to be clustered into 3 categories of cumulative stress, what we will term low, moderate and high. Related to low stress exposure, only one infant experienced a low level of stress and was discharged earlier than other infants. Additionally, only a few infants who experienced higher stress eventually dropped into the low stress cluster. Further analysis of the line graph showed a cluster of infants who experienced a moderate amount of stress and a substantial number of infants experienced high stress during their NICU care.

The second important consideration of the graph is that the overall stress experience for infants did not significantly change over time. Following day one in the NICU, infants appear to remain in their stress cluster for the entire data collection period. Given the lack of significant change from a higher cluster stress to a cluster of low stress, the stress experience can be interpreted as a state of significant chronic stress. Concerning, studies have shown chronic stress to be detrimental to long term outcomes (Joel & Baram, 2009).

The relationships between NNNS neurobehavioral outcomes and stress reveal several worrisome findings. As would be expected, infants who require less supportive care, evidenced by Total Average Stress scores, had lower stress scores and better neurodevelopmental outcomes than infants who require increased medical care. Those infants with higher Total Average Scores demonstrated worse NNNS scores for self-regulation, physiological stress, and GI stress. While this data is important, without the ability to measure stress real-time during NICU care, we may not be able to tap into the pivotal moments when stress experiences are occurring in order to modify the environment to meet neurodevelopmental health needs.

Conclusion

Little research exists to elucidate specific effect of stress in the NICU. Particularly the dose and type of stressors likely to impact long term outcomes. Also, little is known about the mechanisms underlying individual differences in preterm infant outcomes following extended NICU hospitalization. This study provides novel understanding of the genetic and environmental risk factors of stress on neurodevelopmental impairment in the NICU. To date, there has been no published literature examining the potential relationships between the physical and psychosocial stress associated with the NICU experience and polymorphisms of the stress-susceptibility gene FKBP5. Elucidation of these potential relationships will allow for further exploration of gene x environment interactions and ultimately to design neuroprotective interventional strategies. The ultimate goal for research that identifies molecular differences in how individuals perceive medical care experience would be to

develop evidence-based practice initiatives to protect those that are most vulnerable due to the combination of genetic susceptibility to stress and medical fragility.

Limitations

Several limitations should be considered when bearing in mind these study findings. First, as an exploratory genetic study the sample size is small and thus restricted our ability to conduct some analyses, including haplotype analyses. Second, due to the low number of infant carriers of the minor allele, we lacked statistical power to analyze the 3 genotypes individually. Third, due to the nature of the NNNS summary score data, the lack of an overall score NNNS score or consistent type of data among the summary scores restricted the analyses able to be performed. Finally, due to the variation in the time of day births occur, day 1 of NISS data collection was challenging to analyze.

Implications for Practice

While a larger sample is needed to validate these results, preliminary results indicate there is a genetic vulnerability to early life stress predictive of neurodevelopmental outcomes prior to NICU discharge. If confirmed, the implications for clinical practice are tremendous. First, stress scores in the NICU currently do not exist. However, as evidenced by these study findings, real-time stress scores may be a critical measurement, in conjunction with clinical judgment, needed to provide caregivers with the data to understand infant risk from cumulative stress experiences.

Second, because this data identifies a genetic vulnerability to stress from medical care, we now have evidence for why NICUs must rethink how infant care is delivered. Almost one-half of the infants in this sample carry at least one copy of the risk allele. Coupled with the evidence of genetically linked neurodevelopmental vulnerabilities, this

suggests that a large proportion of NICU infants are at increased neurodevelopmental risk. Because we do not know the genotype of infants in the NICU, we must care for all infants as though they carry a risk allele, thus are at heightened risk for poorer long-term outcomes.

Third, if experiences of intense stress have been identified for older persons as situations of potential trauma, with this stress data, we too must recognize and validate the NICU infant experience as potentially traumatic. In doing, we open the door for the opportunity to deliver trauma-informed age-appropriate care (Coughlin, 2014). The implications to delivering trauma-informed NICU care include: 1) how caregivers are educated to deliver care to vulnerable infant and, 2) change in the eligibility criteria for early intervention support to include a broader population of at-risk infants.

Lastly, if validated in a larger sample, this data will necessitate clinical practice to include care interventions that moderate the infant experience. Until such interventions are fully integrated into standard and routine practice, interventions should be ordered for patients in the medical record, similar to how laboratory specimens are ordered. For example, supportive interventions such as skin-to-skin holding and parent delivered care should be ordered interventions. Other developmentally supportive NICU interventions, historically integrated into practice based upon the culture of a unit, therefore suggestive for clinical practice but not required, must become requirements of *all* units. These interventions include developmentally appropriate levels of light and sound in the nursery, pain management strategies and how parents and families are integrated into care. Again, if the evidence indicates that infant perception of stress, based upon genetic sensitivity, influences short-term neurodevelopmental outcomes, and the NNNS is

predictive of longer-term outcomes, then we may now have evidence of an important mechanism influential in the long term brain health of NICU infants. Moving forward it will be critically important that we integrate into clinical practice a very clear understanding of how influential our work in the NICU is to long-term outcomes. No longer can we believe that each intubation attempt, heelstick or missed opportunity for parent holding matters for that moment, this data suggests the impact may last for a lifetime.

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CHAPTER 5.

Imperative Initiatives for a NICU Paradigm Shift

Imperative Initiatives for a NICU Paradigm Shift

Do all infants need to be genotyped in order to know whom to provide developmental sensitive care that is supportive of a resilience outcome? The answer to this question lies in the context within which it is asked, albeit a research or clinical perspective. From a research perspective, *yes*, we need access to genetic samples from many infants, at least until we understand more about the genetic vulnerabilities for medically cared for infants. From a clinical perspective, *no*, care needs to be delivered to **all** infants based upon the premise that all are “potentially vulnerable.” This chapter begins with a discussion of risk from genetic susceptibility and then examines the effects of stress on neurodevelopmental outcomes followed by research considerations. Lastly, the implications for practice will be discussed.

Genetic Susceptibility

As depicted in the framework of *Infant Medical Trauma in the NICU*, Chapter 2, genetic susceptibility is an important factor in the health of NICU infants. The study discussed in Chapter 4, *FKBP5 Genotype and Early Life Stress Exposure Predict Neurobehavioral Outcomes for Preterm Infants*, identifies molecular differences as a predictor of infant response to stress. This research is the first to demonstrate both descriptive findings of stress in the NICU and genetic susceptibility in relationship to measurements of short-term outcome. Many more research studies will be needed to construct a broad foundation of knowledge about the influences of stress associated genes and gene combinations on important infant outcomes. These studies will include not only evaluations of genotype susceptibility, but also epigenetic understandings of how gene

expression may be modified based upon the varied and possible environmental exposures experienced within early life medical care in the NICU.

Studies that examine stress over time, and corresponding methylation changes may provide biobehavioral evidence of when stress reactivity changes from an acute state to one that is chronic. As evidenced in Chapter 4, given that the intensity and chronicity of stress is an important factor in health, this would be an important area to continue to study. While stress is a multifactorial trait, the identification of poorer neurodevelopment outcomes at discharge related to stress and genotype must propel investigators to identify, along the continuum of NICU stress, when one's allostatic load becomes burdensome and impacts the state of health. In addition, more studies are needed that examine these long term effects over time as the infant develops into toddler, child and even into adulthood. An increasing number of research opportunities are needed to better understand the genetic susceptibility of medicalized infants in the NICU.

Stress- the 6th Vial Sign

If the first step in this process is to understand the molecular threshold of stress that tips the balance from benign to iatrogenic, the dose response of stress, the second step is what to do with that data. Specifically, determination of stress cutoffs will be crucial to the translation of this work into clinical practice. For example, creating environmental modification strategies, or stress zones, that provide caregivers with intervention strategies for lowering the stress experience when infants are at-risk from their experience.

While infant medical care in the NICU varies based upon particular needs, all infants are exposed to some amount of basic routine care in the NICU, categorized as low

NISS stress in the aforementioned research. Arguably, depending upon the state of infant illness and gestational age, the individual infant response to low stress may be different from infants who may be in more vulnerable states of illness or age. The NISS as it is currently designed does not capture this variance.

The NISS data collection instrument incorporates many components of procedural care in the NICU. Examples of typical care interventions and the corresponding stress scores are shown in Table 1. As expected, increased medical care needs of the infant result in increased stress scores. Currently scores are captured daily and summed over time but that does not capture the changing neurodevelopmental status of the infant. And although the score is cumulative, it also does not capture infant response and as such does not provide a measure of when the stress is too great except as a comparison to stress associated with routine care or during procedures. The infant's stress response is much more difficult to capture and is often multi-factorial.

Despite the current lack of a NICU stress scores measurement with associated environmental modification options, there are ways for caregivers to begin making potentially important caregiving changes. As discussed in Chapter 3, utilizing interventions such as: skin-to-skin holding, parents as caregiving partners, critical thinking to support delivery of individualized developmental supportive care as well as management of the caregiving environment.

Table 1. Sample NISS Scores.

Healthy infant	Preterm infant with feeding support	Preterm infant with respiratory and feeding support, IV access and blood work twice
Diaper change 6 times/day ³	Diaper change 8 times/day ³	Diaper change 8 times/day ³
Position changes- 6 times/day ³	Position changes- 8 times/day ³	Position changes- 8 times/day ³
Daily weight ³	Daily weight ³	Daily weight ³
Undressing/unwrapping for weight ³	Undressing/unwrapping for weight ³	Undressing/unwrapping for weight ³
	Gavage feeding 8 times/day ³	Gavage feeding 8 times/day ³
	Indwelling nasogastric tube ²	Indwelling nasogastric tube ²
	Aspirate check 8 times/day ²	Aspirate check 8 times/day ²
		Receiving CPAP ³
		Nasal suctioning 6 times/day ⁴
		Insertion of IV ⁴
		Indwelling IV ²
		Heelstick 2 times ⁴
Total stress score= 42	Total stress score= 100	Total stress score= 166

Superscript indicates stress category.

Research abounds of the many benefits of skin-to-skin holding, for both parents and infants. This intervention requires no technology or equipment, it is completely free of charge and typically has very willing and eager participants. This is not to say that transitioning a fragile infant from bed to parent is always easy, however it is one of the most basic interventions that can have such meaningful results for both parties. Rather than considering skin-to-skin a *nicety*, all caregivers must reframe the purpose of skin-to-skin into an imperative intervention that should be offered to parents and infants at least daily. Occasionally this is not possible, however this supportive caregiving for the infant and parent should be our goal.

Including parents as caregivers into their infant's medical care needs is vitally important as well. Most parents are willing and capable to participate in caregiving activities beyond a diaper change and temperature assessment. Most often parents provide a calming and less painful approach to care that infants respond to. Additionally, parents' typically benefit greatly from being able to learn how to care for their infant in the NICU; increasing their competence for caring for these infants after discharge.

Caregivers must embrace their own ability to critically think and reflect at each infant encounter. Rather than applying a standardize approach to each and every caregiving experience, identifying the important needs for the individual infant, at that very moment, may create an opportunity to modify an infant's stress experience. Performing procedures that may not improve caregiving or truly benefit the infant should be reconsidered. Examples may include: suctioning an infant every 3 hours because that is your standard of care, yet the infant has minimal to no secretions; performing heelsticks for bloodwork that ultimately will not change the course of care, rather is just another number in the chart. Recently, an initiative called "choosing wisely for newborn medicine" has been examining unnecessary caregiving costs and making recommendations for changes. Although these two caregiving procedures are not among the top five recommended they remain areas where we can "choose wisely" (Ho et al., 2015)

In many NICUs the volume of sound and brightness of lights far exceed what is beneficial for infants. Often caregivers are bothered by the noise and light in our units, consider what those same sensory experiences feel like to a sick infant. The environments of the NICU have been created to support the medical caregiver and need

to be further redesigned to better support the infant and family. A nurse on a medical-surgical floor for adults or children would never consider leaving the bright overhead lights on when a patient is trying to sleep, or talk in volumes most appropriate for personal conversations yet these activities occur regularly in the NICU. Furthermore, they would never “flip” a sleeping patient over and provide care without taking the time to wake the patient and tell them what procedure needs to be conducted. Yet, in the NICU these practices occur as routine aspects of care. Considering the high level of early stress experienced by infants in the NICU as demonstrated in Chapter 4, caring NICU professionals need to provide care that better supports neurodevelopmental outcomes.

Infant Medical Trauma in the NICU

The opportunity that exists before us, to assign a term of significance to the infant NICU experience, has the potential to serve many purposes. By using our knowledge of the data that suggests that a sizable proportion of infants may be susceptible to the stress exposure associated with medical care, as evidenced by poorer neurobehavioral outcomes, we are providing validation that the infant experience of newborn intensive care may be traumatic. While infants cannot verbalize their personal symptoms resulting from an intense stress exposure, we can utilize biobehavioral data as a proxy. These data are similar to what is used in verbal populations, to demonstrate physiological evidence of trauma exposure such as cortisol reactivity. For infants in the NICU, use of genetic susceptibility and stress data to predict neurodevelopmental outcomes has the potential to begin thoughtful discussions and conversations about the meaningfulness of these experiences to individual infant.

Implications for Practice

Some NICUs do an outstanding job of assessing neurodevelopment during NICU care, in turn, using those assessment findings to individualize care to support infant outcomes. However developmental care that is truly individualized like personalized precise medicine is not routinely practiced as the standard of care across all NICUs. The information gained from neurodevelopmental assessments is critically important to understand how the vulnerable infant brain is organizing extra-uterine life experiences. Furthermore, when assessed more than once over the course of NICU care, enhanced knowledge of behavioral organization trends and changes may be gleaned, allowing for even greater individualized care. Following discharge from the NICU, this data can then be shared with community providers for tracking neurodevelopmental progress as the infant ages.

Prior to environmental exposures that result in observable infant neurobehavioral changes, those at the point of care must be well versed in reading and interpreting infant behavioral cues. At this point in time, in many NICUs, the expertise of behavioral assessment lies with a developmental specialist. While there are intricate aspects to understanding the cues of infants, this knowledge is imperative to providing sound neurodevelopmental individualized care. The ownership of this knowledge must be broadly shared with those on the front lines, those who interact minute-by-minute with NICU infants. Particularly, nurses need to use the behaviors of the infants to guide their caregiving decision-making. Furthermore, we must use this knowledge to benefit our patients. Interestingly, in Liu et al. (2010), through NNNS assessment, infants who would not have otherwise been identified as at-risk, based upon medical and demographic

characteristics, were identified with concerning behavior. This points us towards recognizing that even though an infant may not be diagnosed with an intraventricular hemorrhage when in our care, that does not mean they have escaped NICU care unscathed (Jarjour, 2015).

When confronted with an individual who speaks a language different from our own, it is incredibly challenging to communicate. The same is true when communicating with preverbal infants- it is a learned language. When nurses and other caregivers cannot accurately interpret infant cues, tone and state regulation we are only providing partial care. Our goal should never be to provide partial care; our goal should be optimal individualized care. This brings to mind the future of healthcare- personalized medicine.

The goal of personalized medicine is to one day tailor treatment and care specific to one's particular genetic make-up. While genotyping all NICU infants in order to learn how vulnerable they may be to the NICU experience is not an impossible task, for now it is an expensive one. The alternative, and relatively inexpensive, is to treat all infants who enter the NICU as though they are at increased risk from their stress exposure and genetic susceptibility. By combining increased awareness of an infant's stress experience and improving our current NICU model of care to include parents as care providers, within the underlying genetic context of an infant, we may very well see gains in decreasing long-term neurodevelopmental risks. Importantly, the long-term health of infants cared for in NICU may be entirely linked to how they are cared for in their early days of life. As such, NICU providers must embrace the incredible responsibility of caring for such a vulnerable population and practice in a manner that is fully aware of not only care needs

in the moment, but possibly even more important, the potential that a lifetime of consequences are possible because of the care received within the NICU doors.

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