

Gravens By Design: Six Weeks that Changed the Preterm Infant Brain: Insights from the Family Nurture Intervention (FNI) Randomized Controlled Trials

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Abstract:

Our group conducted two randomized controlled trials over 12 years between 2008 and 2020 (total n=261) comparing neonatal intensive care unit (NICU) standard care (SC) with SC plus Family Nurture Intervention (FNI) of infants 26 to 34 weeks GA. The intervention included ~6 hours per week (24 to 36 hours total) of facilitated mother-infant calming sessions aimed at dyadic "emotional connection" during the NICU stay. At approximately 35 weeks and 41 weeks postmenstrual age, we collected electroencephalographic (EEG) activity on the brains of all subjects using 128-lead nets. Analyses at near-term age showed dramatic changes in brain function on multiple measures in FNI vs. SC infants. Importantly, we found similar increased prefrontal cortical activity in a multisite replication trial of FNI-NICU. We have documented in 18 publications that FNI group infants had significantly better short- and long-term neurobehavioral functioning, autonomic health, and developmental trajectories. FNI dyads had significantly better autonomic regulation than SC dyads through five years. In this article, we discuss the key features of FNI that led to our results and the theoretical and clinical advances that grew out of the trials. We discuss how these insights can help improve preterm infant outcomes. We introduce new terminology and constructs that describe behavior and physiology and a new assessment tool that correlates with physiology to measure the mother/infant emotional relationship (Welch Emotional Connection Screen). Finally, we discuss the significance of our findings and how our insights might be incorporated into other NICU interventions and widespread standard NICU care.

Keywords: attachment; emotional connection; approach-avoidance; brainstem; instinct; state-trait; conditioned reflex; Infant development; autonomic conditioning

Background:

Our group tested the efficacy of Family Nurture Intervention (FNI) in a level-4 neonatal intensive care unit (NICU) at New York Presbyterian Morgan Stanley Children's Hospital single site in a randomized controlled trial (RCT) between 2008 and 2012. We replicated the intervention in a multisite RCT (New York Presbyterian and UT San Antonio) between 2016 and 2020. FNI was designed to increase specific activities that enhance the emotional connection between mother and baby. (1) Our primary objective was to

determine whether repeated mother-infant calming sessions that included maternal emotional expression would improve the infant's developmental trajectory.

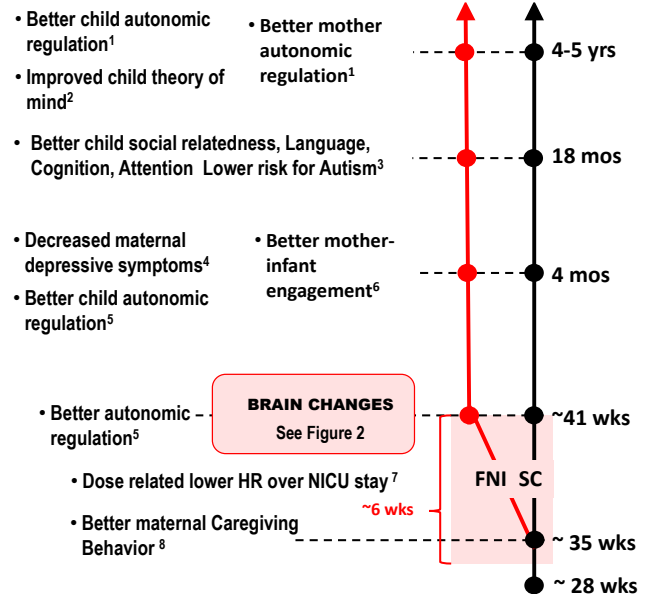


Figure 1 - Published findings from two RCTs of Family Nurture Intervention. FNI was conducted in level 4 NICUs. The intervention period is shown in blue. Note that findings included both behavioral and neurophysiological outcomes.

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Thus far, our group has published 18 outcome papers comparing a group receiving Standard Care (SC) with a group receiving Standard Care plus FNI. Compared to controls, FNI infants showed significant improvement in neurobehavioral functioning, autonomic health, and development, FNI mothers showed significant improvement in depressive symptoms, and the dyad scored higher on relational and physiologic health at key assessment points through age 5 (**Figure 1**).

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The most dramatic effect of the intervention was in changes in brain function (**Figure 2**). Fortuitously, our NICU was the beta site for developing high-density 128-lead nets, enabling us to collect a wealth of data. At the beginning of the first trial, one of our neonatologists, who had been conducting EEG studies on preterm infants for decades, confidently stated, “We will never see changes in EEG over six weeks in the NICU.” When the first study showed significant increases in prefrontal cortex EEG activity after the six-week intervention period ($p < .0001$), he not only conceded but advocated providing this intervention to all babies, even those born ultra early.

The large preterm infant data set attracted the attention of a world-renowned EEG expert Sampsa Vanhatalo, who was pioneering a new method for measuring infant brain networks. Using our EEG data from the first trial, Dr. Vanhatalo and his colleagues could show several large-scale, frequency-specific network effects of FNI, most extensively in the alpha frequency in frontocentral cortical regions. (2) The findings at term age were comparable to healthy full-term-born infants. Notably, the connectivity strength in this network correlated with the later neurocognitive performance of the FNI group at 18 months. These findings suggest that preterm brain development can be significantly improved by facilitating emotional connection between mother and infant. We are continuing to analyze data, and several more papers are in preparation.

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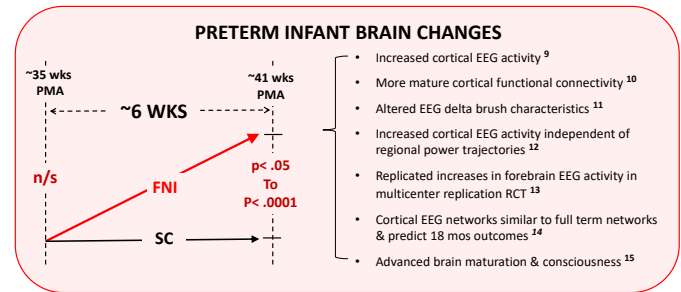


Figure 2 - Six weeks that changed the preterm infant brain. In six weeks, between approximately 35 weeks and 41 weeks, we collected high-density 128-lead electroencephalographic (EEG) activity on the brains of all subjects. Analyses showed dramatic changes in brain function on multiple measures. Importantly, in a multisite replication trial of FNI-NICU, we found the same increases in prefrontal cortical EEG activity.

At this point in the follow-up of the FNI trial cohorts, we can confidently say that mother/infant dyads in the FNI group benefited significantly from the intervention. Additionally, because the intervention dose was relatively small, and the effects on the dyad persisted for so long, we feel it is essential to examine the factors we believe led to the results more closely. Therefore, in this article, we will address some crucial questions such as:

- What features of the intervention led to the outcomes?
- How is FNI different from other NICU interventions?
- What are the key biomarkers associated with the FNI changes?
- What are the biological mechanisms underlying FNI?
- Can FNI be integrated into standard NICU care?
- Is FNI scalable?

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What is Family Nurture Intervention

Mothers assigned to the FNI group agreed to attend at least four 1-hour intervention ‘calming sessions’ per week while in the NICU. Mothers who came to the NICU more frequently were encouraged to engage in intervention activities more often and for longer periods. Calming sessions between mother and infant included skin-to-skin contact, odor exchange, firm, sustained touch, eye contact, and oral communication. These activities are used regularly in other NICU interventions to improve infant and maternal outcomes. However, the key activity encouraged during the 60- to 90-minute FNI ‘calming sessions’ was ‘emotional expression’ between mother and baby accompanying sensorial contact in the isolette or during holding or skin-to-skin sessions. To our knowledge, FNI is the only intervention that focuses narrowly on emo-

tional expression as the critical element in changing the mother/baby's emotional relationship.

The calming cycle

The central activity of FNI-NICU trials was the 'calming cycle' (see Figure 2). The phenomenon was first described in Holding Time. (3) Welch discovered that if the mother held the child until their upset was resolved regularly, communication between the two improved, upsets occurred less often, symptomatic behavior declined, and the emotional relationship and child development improved.

We applied the same theory in the NICU. The idea behind the NICU intervention is that repeated close physical and emotional communication between the mother and baby will result in calmer states of behavior and physiology (homeostasis) (Figure 3) and emotional connection.

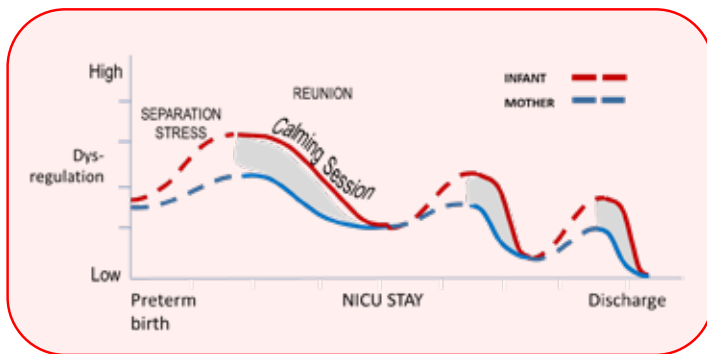


Figure 3 - The hypothesized NICU calming cycle. Separations increase upset and dysregulation in both the mother and the infant. One-hour calming sessions lead to calm behavior and calm physiology. Repeated sessions lead to more rapid reductions and lower absolute levels of upset and dysregulation in both the mother and the infant.

FNI focused on enabling mothers to engage in specified mother-infant interactions as early as possible after birth, within the constraints of the NICU environment. These interactions began while the infant was confined to the isolette, later during skin-to-skin or clothed holding, and near discharge during family sessions when strategies were developed to support the mother as she continued these interactions with her infant at home. The maternal-infant interactions included odor-cloth exchange, firm sustained touch, vocal soothing, eye contact, and emotional expression.

Emotional expression

Due to the long-term hospitalization and uncertain prognosis of preterm infants, mothers experience strong negative emotions, such as fear, frustration, stress, anxiety, and guilt. Many strategies are now in place to support and help mothers cope with the NICU experience, such as Family Centered Care, Skin-to-skin Care, parent support and education programs, Interpersonal Therapy, spiritual care, NIDCAP, and telenursing. (4, 5) FNI employed some of these strategies. However, the central feature of the FNI-NICU method was helping the mother express strong emotions directly to the infant, which can be different from how she might express emotions and other social information to others in the variety of contexts that make up her everyday life. (6) To avoid confusion, the strategy employed in the FNI-NICU trials is called *Welch Emotional Expression (WEE)*.

Nurture specialists (NS), in this case, former NICU nurses, facilitate mother/infant emotional expression during 60 to 90-minute calming sessions. The NS did not attempt to teach or educate the mother about the intervention before she felt a connection with her infant. Instead, the NS helped the mother engage emotionally with her baby from the start. The first calming session typically took place at the isolette, on average, one week after birth. As early as the first session, the mother was encouraged to express deep emotions and feelings directly to her baby.

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Sometimes the mother was emotionally blocked and had difficulty accessing her emotions with her baby. In these cases, the NS created as much privacy as possible for the mother and baby and suggested things the mother could say directly to her baby. For instance, the NS said to the mother, 'Tell your baby the birth story,' 'Tell your baby how you felt when you got pregnant,' 'How you felt when you were told the baby was going to be premature,' etc. The feeling of 'guilt' in NICU mothers is often overlooked. (5) One particularly effective prompt the NS used to help the mother release her emotions was to suggest the mother apologize to the baby and say something like: 'I am sorry for the separation and for the suffering you are going through.' This apology often prompted an emotional response from the mother and allowed the mother to cry.

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Crying is one of the deepest, most powerful, and most therapeutic emotions a mother can express to her baby in the NICU. (7, 8) It is common for the mother to hold back crying. Sometimes, the mother is told not to cry by friends and staff, 'Everything is going to be OK.' Sometimes, the mother releases her emotions to the staff of family members. With FNI, crying with her infant was anticipated and welcomed. However, the NS told the mother to direct her emotions to the baby and let herself cry while holding her baby whenever she felt like it.

Such release of emotions by the mother while holding her baby prompted the baby's primary *orienting reflex* typically (9) (more on this phenomenon below). Orienting includes turning toward

the mother and making direct eye contact with her. When this happens, the mother typically feels an emotional connection to her baby, most often for the first time. The NS encouraged the mother to emotionally interact when touching her baby in the isolette or holding the baby during skin-to-skin or clothed holding. The nurture specialist encouraged the mother not to use her cell phone during her brief time with her baby. The mother was encouraged to direct her attention and emotional feelings to her baby—not to the nurture specialist, family members, or nursing staff.



Figure 4 - The key to Family Nurture Intervention in the NICU

The mother was also asked to speak or sing to her baby in her 'native' tongue (i.e., the language her grandmother spoke to her mother (or to her) when she was a baby). This is because the emotional content of expression between the mother and baby is most effectively conveyed in the primary language. (10, 11)

Our clinical observations confirm that once the mother releases her emotions to the infant, the infant becomes more available to the mother and responds behaviorally through eye contact and approach behaviors (Figure 4). This response from her baby profoundly moves the mother and prompts approach behaviors from the mother. The repeated emotional expression between the mother and infant during the NICU stay changes the dyad's emotional relationship and positively alters the infant's developmental trajectory and the mother's emotional well-being.

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How does FNI differ from other NICU interventions?

FNI overlaps in some ways with many current mother-infant interventions implemented in the NICU that have been shown to improve some outcomes, such as kangaroo care (KC)(12), kangaroo mother care (13-15), developmental care (16-18), Parental emotional support by nurses (4), couplet care (19), to name a few. Such interventions have in common the importance of bringing the mother and preterm infant together as soon as possible following birth, assuming that proximity and contact will improve outcomes. Such proximity and contact are, of course, known to be necessary and critically important, but they do not assure an adaptive emotional relationship. FNI takes skin-to-skin contact a further step in engaging the mother and infant in emotional exchange. In addition, FNI differs substantially on the theoretical biological basis of the mother-infant relationship.

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mental care, promote mother/infant 'co-regulation.' However, such interventions are equivocal regarding the mechanisms involved.

What is an emotional connection?

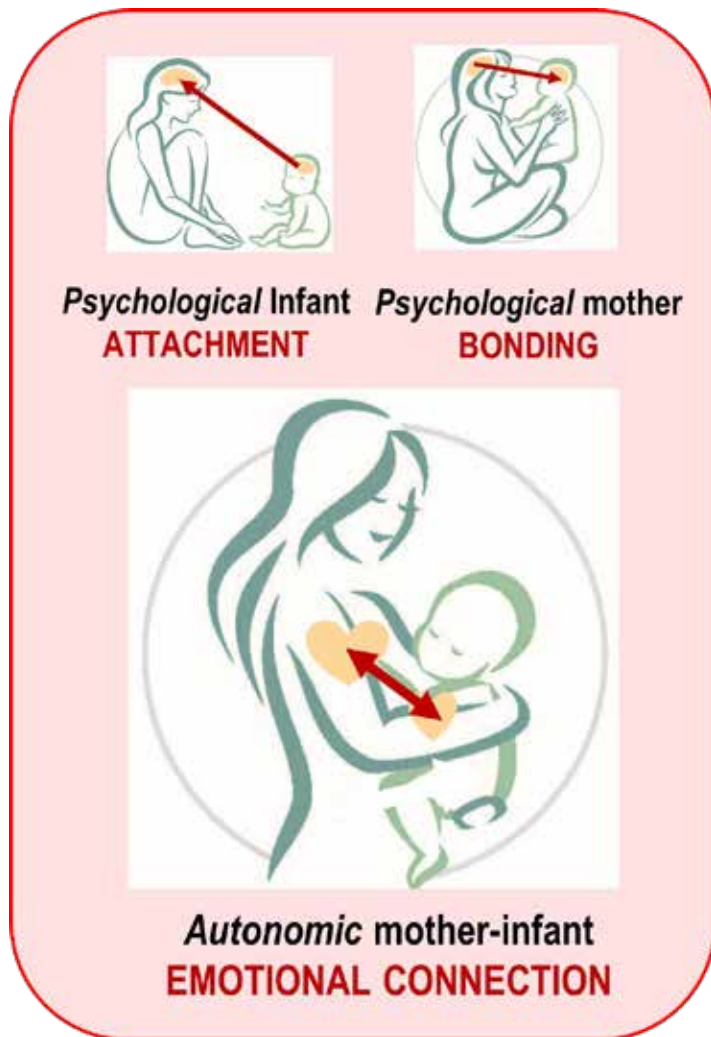
The most important concept that was supported by FNI-NICU trials is *emotional connection*. Emotional connection is an 'autonomic' construct—that is, it has to do with the autonomic nervous system, the nervous system that controls internal organs, especially the heart. Emotional connection describes the special biological relationship between a mother and a newborn infant. The emotional connection model differs from prevailing 'attachment' and 'bonding' models in how it views the early mother-infant relationship. The attachment model posits that the baby is born with behaviors toward a *mother figure*. (20, 21) Thus, the mother is not substantially differentiated from other caregivers.

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preterm babies are born with a special *autonomic relationship* with the mother that requires repeated mutual mother-infant learning and reinforcement. The basics of emotional connection theory were articulated in the FNI study protocol (1), but the theory has been more thoroughly and carefully explicated since then. (10, 22-24)

Viewing the mother and infant relationship in terms of autonomic emotional connection requires rethinking the biological mechanisms mediating the phenomenon (Figure 5). Conventional constructs like attachment and bonding focus on cortical learning mechanisms. In contrast, emotional connection theory posits that mother/infant emotions are controlled by a highly conserved primitive learning mechanism outside of consciousness within the autonomic nervous system. A central tenet of emotional connection theory is that specialized primary cardiac reflexes form between mother and fetus via autonomic learning (conditioning) during gestation. (25) Pavlov termed this mechanism the conditional 'cardiac' or 'social' reflex. (26) 'Conditional' reflexes account for so-called mother and infant subconscious "instinctive" behaviors following birth. The term 'conditional' infers that the behaviors associated with the reflex depend on various environmental factors or conditions. For instance, in a normal birth, the social signaling between the mother and baby assures 'approach' behavioral responses. In preterm birth, however, the critical social signaling is disrupted between the two, often resulting in adversely conditioned 'avoidance' behaviors.



The autonomic reflex construct originates in a phenomenon ini-

Figure 5 – Emotional Connection vs. Attachment and Bonding. Note that emotional connection communication is heart-to-heart. Attachment and bonding are brain-to-brain.

tially described by Pavlov in 1925 (27) when he described how a social relationship could profoundly impact the cardiac reflex (and associated behavior) below the conscious level. We have extended this basic concept to the mother-infant relationship and termed it the *autonomic socioemotional reflex (ASR)*. (25)

The term ASR applies specifically to neonatal mother-infant physiology related to the well-researched *orienting reflex*. (9) Orienting disorders are highly correlated with socioemotional pathologies in infants and children, such as social fear, anger, anxiety, depression, and autism. (28) Orienting stems from the activation of highly conserved autonomic defensive and appetitive motivational systems that evolved to sustain life (29) and assure species' survival. (30) In this respect, humans' mother/infant ASR orienting phenomenon does not differ significantly from the orienting reflex in other species.

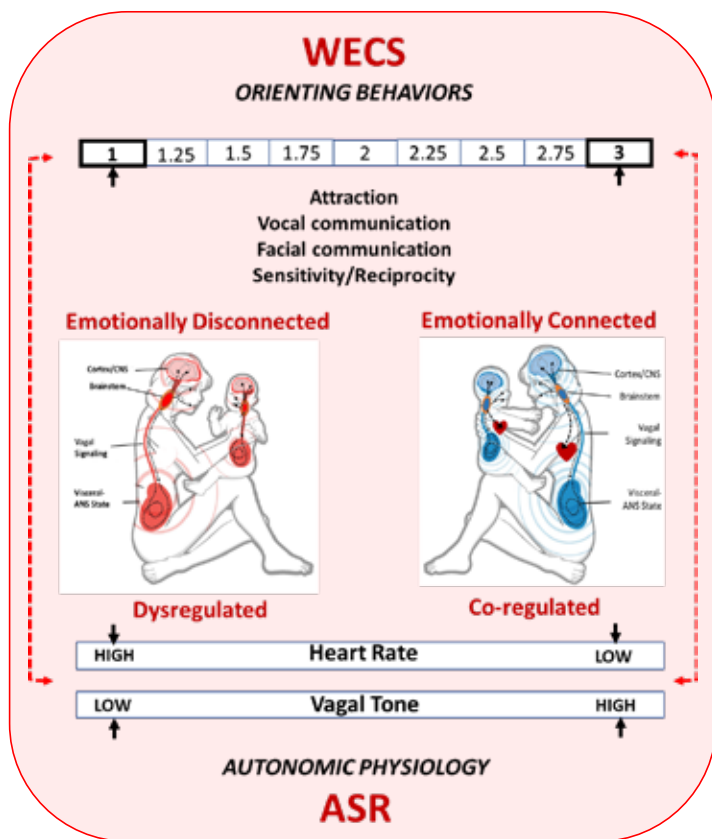
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The ASR is theorized to correlate with the dyad's mutual autonomic 'states' at the time of observation, as opposed to their assumed individual 'traits.' Emotional connection theory predicts that negative *traits* are *states* created by negative environments. Therefore, if the baby's primary environmental signals are changed (e.g., through maternal emotional expression), then the baby's behavioral traits can be changed from negative to positive. This observation in the clinical practice of Welch's first iteration of FNI allowed us to reconsider mother/infant approach-avoidance behaviors considering and testing the theorized correlation between dyadic emotional behaviors and autonomic physiology, such as heart rate and heart rate variability. Emotionally 'disconnected' behaviors would correlate with higher HR and lower HRV. Emotionally 'connected' behavior would correlate with lower HR and higher HRV. We used face-to-face observation and later created the Welch Orienting LapCheck paradigm(31) to measure mother/infant behaviors before and after the FNI intervention to test the mother and infant's autonomic emotional reflex reaction to one another. Results confirmed that FNI was changing avoidance behaviors to mutual approach behaviors. (32)

How do you measure the mother-infant emotional connection?

The emotional connection behaviors require a special assessment. In the first FNI trial, we used conventionally validated assessment tools based on the attachment and bonding constructs. Such tools typically measure the separate *psychological* behaviors of the infant and mother but not the dyad's emotional *relationship*. As the trial progressed, we observed significant positive changes in the emotional relationship between the mother and the baby.

Based on her clinical observations in the 1970s, Welch had predicted that a few key behaviors could form the basis for a simple tool that would reliably assess the emotional relationship between mother and infant and identify dyads at risk for socioemotional disorders later in development. Such a tool could be used as a screen to identify dyads needing help and demonstrate the efficacy and effectiveness of an intervention. This led to the Welch Emotional Connection Screen (WECS) development. The process resulted in a subset of four observable mutual mother/infant behaviors: *attraction, vocal communication, verbal communication, and sensitivity/reciprocity*. Hane, an expert in coding approach behaviors, vocal rhythms, and mother-infant affect (33, 34), validated the WECS construct by comparing WECS behaviors using conventional labor-intensive observational coding software and correlating infant biobehavioral responses to the mother-infant in a still-face paradigm. (32)



As predicted, these behavioral subsets correlated with the mother and infant seeking a mutual approach to each other following *Figure 6 - WECS Behavior & ASR Physiology relationship*. Schematic showing the hypothesized mirror reflection of WECS behaviors and autonomic socioemotional reflex (ASR) physiology. The two sets of WECS behaviors at the opposite ends of a 9-point Likert scale are illustrated at the top of the figure. Shown at the bottom is cardiac physiology that correlates with WECS behaviors. Therefore, the WECS assessment serves as a quick and straightforward behavioral mirror reflection of autonomic physiology, which can inform immediate intervention.

stress and the preterm infant's autonomic state physiology (cardiac response to stress)(32) (**Figure 6**). These data suggest that the mother/infant emotional connection is a behavioral mirror of the dyad's autonomic response to close physical face-to-face

proximity and a vital indicator of the dyad's emotional relationship at the time of observation. The clinical and practical advantage of the WECS is that it offers a fast, simple behavioral assessment screening measure that can assess risk for impaired socioemotional and relational health. FNI study results confirm the benefits of detecting and treating breaks in the early emotional connection between mother and infant.

The practical utility of the WECS

NICU Emotional connection, as described here, provides NICU clinicians and researchers with a new framework for evaluating the mother-infant relationship. The WECS, because of its demonstrated accuracy and reliability, makes a useful additional tool in the NICU for clinicians and researchers (**Figure 7**). The ability to assess information quickly means that the information is 'actionable.' Clinicians practicing a wide range of mother-infant interventions, such as skin-to-skin care, developmental care, family-centered care, etc., can incorporate new ways to sensitively intervene that help the mother express her emotional feelings directly to her baby.

The FNI-NICU is not a prescribed intervention. There are many ways to help mothers open up to their babies and become emotionally connected. Instead, the insights gained from the trials should be taken as a guide for what to look for and what the goal should be. The trials have demonstrated what is possible.

Welch Emotional Connection Screen (WECS)

Quick
Reliable
Predictive
Actionable

Post-NICU

The WECS is being incorporated into the clinical practice of col-
Figure 7 - Strengths of the WECS

leagues in NICU follow-up clinics. The WECS is also being studied in the residency training program at Emory Developmental Pediatric. (35) O'Banion et al. showed that resident accuracy for identifying dyad emotional connection on the WECS improved significantly following brief training. As well, residents reported significantly changed beliefs about the importance of improving their ability to assess emotional connection and incorporating emotional connection assessment into pediatric practice.

We recently completed a novel family-based preschool intervention using the WECS to determine whether a parent-child home intervention, *E-Prep*, could improve classroom behavior. WECS scores of E-Prep children correlated with significant improvement in socioemotional and classroom behavior. (31)

Summary:

The Family Nurture Interventions testify to the plasticity of preterm infant developmental mechanisms. (36) Following the intervention

over six weeks in the NICU, the brain network function of FNI infants resembled the function of term infants. As much as both SC and FNI received the same SC, we believe these changes resulted from facilitating the emotional connection between mother and infant.

A recent review of the literature confirms that despite a growing body of mother-infant research citing Bowlby's theoretical constructs of psychological 'attachment,' 'bonding,' and the associated variables, there is little agreement on the definitions of the constructs, as well as a lack of a comprehensive conceptual framework of antecedents and consequences of constructs that can guide empirical work. (37, 38) In addition, attachment treatment models have proved difficult to scale. (39) Conversely, there are notable shifts in current early intervention paradigms(40) and growing evidence supporting a new autonomic framework. Recent studies confirm the importance of a mother's breast odor and voice in enhancing the orientating response(40) and motivational seeking effect(41) on infants. (42) A recent study showed that modifying the position of mother-infant skin-to-skin care led to more overall communication between mother and preterm infant, a three-fold increase in vocalizations, more eye contact, and more smiling,(43) which suggests such proactive interventions help the mother and infant connect emotionally.

The emotional connection construct offers a new way of viewing the mother-infant relationship in the NICU. The FNI-NICU trials provide compelling evidence that the mother is more than an attachment *mother figure*. Rather, the mother-infant relationship should be considered an essential building block for future socioemotional relationships. The mother-infant emotional connection is and should be considered, foundational in overcoming the trauma of preterm birth and establishing healthy and adaptive development.

The field is currently at the threshold of significant discoveries regarding how the brainstem structure exerts varied and significant influences over brain function and behavior. (44)

Emotional connection theory provides a learning mechanism, a theory of change, and a set of testable hypotheses. The theory states that early relational behaviors between mother and newborn are learned through autonomic conditioning of autonomic socioemotional reflexes (ASRs) formed during gestation via autonomic co-conditioning that is stored as conditional reflexes within the dyad's autonomic nervous systems. These reflexes are preserved transnationally and can be used to monitor mother-infant relational health. The autonomic co-conditioning mechanism can be exploited to change the physiological/behavioral reflex response.

Importantly, including mother-infant emotional expression in other types of NICU intervention does not take further resources. Therefore, exploring this promising –and evidence-based pathway might benefit the field. In doing so, the fields of Neonatology and Pediatrics, in general, will attain a more holistic, foundational, and integrative approach to interventions and research, which could positively impact neonatal treatments and clinical outcomes. (45)

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