Early Human Development 127 (2018) 6–14

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Human interaction in the NICU and its association with outcomes on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA)

Gonya J.[a,*,1], Feldman K.[b,1], Brown K.[a], Stein M.[a], Keim S.[c], Boone K.[c], Rumpf W.[d], Ray W.[d], Chawla N.[b], Butter E.[e]

[a] Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH, United States of America
[b] Interdisciplinary Center for Network Science and Applications, University of Notre Dame, Notre Dame, IN, United States of America
[c] Center for Biobehavioral Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH, United States of America
[d] Battelle Center for Mathematical Science, The Research Institute at Nationwide Children's Hospital, Columbus, OH, United States of America
[e] Department of Psychology and Neuropsychology, Nationwide Children's Hospital, Columbus, OH, United States of America

ARTICLE INFO

Keywords:
Extreme prematurity
Neonatal intensive care
NICU
Social competence

ABSTRACT

Background: Extremely preterm infants represent one of the highest risk categories for impairments in social competence. Few studies have explored the impact of the neonatal intensive care unit (NICU) environment on social development. However, none have specifically analyzed the effects of the care structure the infant receives during hospitalization on later social competence indicators.
Objective: To identify associations between the care structures received by extremely preterm infants in the NICU and scores on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA) post-discharge.
Participants: 50 extremely preterm infants (mean gestational age: 25 weeks during hospitalization; mean chronological age during follow-up assessment: 2 years, 4 months).
Methods: A secondary analysis of BITSEA data was performed exploring its relation to care structure data we extracted from electronic medical records (i.e., how much time infants were engaged in human interaction during their first thirty days of hospitalization and what types of interaction they were exposed to).
Results: Extremely preterm infants spend a considerable amount of time alone during hospitalization (80%) with nursing care comprising the majority of human interaction. Infants who experienced greater human interaction scored significantly higher on the Social Competence ($p = 0.01$) and lower on the Dysregulation ($p = 0.03$) BITSEA subscales.
Conclusion: Human interaction and isolation in the NICU is associated with social competence and dysregulation outcomes in extremely preterm infants. Further research is needed to understand how various NICU care structures including centralized nursing teams, parental skin-to-skin care, and early therapy may synergistically play a positive role in developing social competence.

1. Background

Infant social communication is a complex, dynamic developmental process that encompasses human interactions and experiences that begin at the onset of an infant's ability to detect and respond to incoming stimuli. Unlike term infants, who encounter household environmental stimuli, extremely preterm infants (infants born with gestational ages < 27 weeks) are born and hospitalized in a neonatal intensive care unit (NICU) environment. While essential for survival, the NICU is a technologically-driven, socially maladaptive environment that places infants at a distinct social development disadvantage.

During the course of their admission, infants are attached to extensive tubing and monitoring wires, and are placed in isolettes that further detach them from human interactions. These conditions make even routine care highly demanding for an immature brain, often resulting in dysregulation (e.g., abrupt changes in saturation, heart rate, skin color, motor activity, etc.). In extreme cases “shut-down” behaviors occur, presenting as flaccid body extremities and an indeterminate level of consciousness. Such behaviors are known to deplete the energy reserve required to maintain a regulated, alert state for social input, and

* Corresponding author at: Center for Perinatal Research, Nationwide Children's Hospital, 575 Children's Crossroad, RBIII WB6237, Columbus, OH 43205, United States of America.
E-mail address: Jenn.Gonya@nationwidechildrens.org (J. Gonya).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.earlhumdev.2018.08.010
Received 13 February 2018; Received in revised form 11 July 2018; Accepted 27 August 2018
0378-3782/

come at a cost to the fundamental underpinnings of social communication development [1–3].

This defines NICU trauma [4] and it is well established that early trauma has long-lasting effects on infant physiology and psychology [5]. Understandably then, addressing the adverse developmental conditions of the NICU has become a significant research goal. Several studies have identified the effects of extreme prematurity on later social and emotional problems. Extremely preterm infants exhibit behavioral problems, attention deficit/hyperactivity disorder, and autism spectrum disorders at a rate *two to three times higher* than the full-term population [6,7]. These risks are often attributed to disturbances in brain connectivity associated with cognitive impairment [8] that have patterns that suggest origins that are environmental, rather than genetic [6]. What is poorly understood in this population is how and when these disturbances occur and what specific disturbances correlate with longer term social and emotional outcomes. Further, although the major research focus has been on medical sequela, there is a smaller body of growing evidence that the absence of key perinatal developmental inputs might also play a crucial role [1,7,9].

Numerous studies have been published demonstrating the benefits of NICU interventions, such as skin-to-skin care, music therapy, massage therapy, and parent mentoring [10–16]. During these interventions, infants become more physiologically regulated and parents become more engaged and experience less stress. However, in these intervention studies, infant social-emotional outcomes are often overlooked with preference toward sensory, motor, and cognitive development. Yet, it is important to consider that, beyond the treatment itself, these interventions remove the trauma of isolation by providing a source of human interaction.

Such interactions represent the foundation of this work, which aims to open the discussion around the potential influence of interactional and environmental factors experienced in the NICU and their relation to infant social and developmental outcomes. We hypothesized that extremely preterm infants spend an inordinate amount of time alone and those who were exposed to significantly more human interaction in the NICU would score higher on social competence measures and lower on dysregulation and ASD measures later in childhood compared to extremely preterm infants with less NICU human interaction.

In this manuscript, we present a comprehensive set of analyses that explore the variability in the human interaction opportunities of extremely preterm infants in the NICU, and their relation to behavioral measures on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA) at age two. We begin with a univariate exploration of statistical and correlational relation of 13 dimensions of care and interaction to various developmental outcomes. However, there is an increasing body of evidence that no single treatment or experience in the NICU can be linked in whole to developmental outcomes [17,18]. As such, the second component of our work approaches the experiences of an infant in the NICU from a mesosystemic perspective, exploring higher-order interactions between clinical aspects of the care environment, and human factors such as the interaction experiences with respect to developmental outcomes. Finally, we conclude with a discussion of the clinical implications of our findings and present a broad set of future research directions.

2. Data and instruments

2.1. Study population

This secondary analysis study was conducted through Nationwide Children's Hospital (NCH) in Columbus, Ohio and was approved as an expedited, waiver of consent study by the Institutional Review Board. The study included all toddlers who had been born extremely preterm, were admitted to the NCH Small Baby Intensive Care Unit (SBICU) between 01/01/2010–11/30/2011, and who participated in a larger study that investigated the screening accuracy of the BITSEA [19] in toddlers that were born at 30 weeks' gestation or less.

In the larger study, participants were recruited from a roster of all infants who met the gestational age criteria, who received care at any of the twelve NCH-owned NICU's, and who attended a Neonatology Clinic follow-up visit. Questionnaires were mailed to roster families and returned to the researchers by stamped envelopes (return rate 53%). Of the sample of 555 children, 50 children had met the criteria for the secondary analysis and their data were analyzed.

Nationwide Children's is a large academic pediatric hospital in the United States with a specific SBICU. The SBICU is a specialized Level-IV all-referral unit staffed by a centralized team of nurses who provide protocol-driven care [20,21] to neonates born at a gestational age (GA) < 27 completed weeks. All patients cared for in this unit are transported from outlying hospitals and directly admitted to the SBICU for care resulting from complications of prematurity including necrotizing enterocolitis (NEC), sepsis, surgical issues, and brain injury.

2.2. Hospitalization data

Timestamped hospitalization data was obtained directly from each infant's electronic medical record (EMR). Beyond standard demographics, data were extracted around three primary elements of infant care and interaction, a) ventilatory support, b) human interactional elements (nursing, parental skin-to-skin care, and occupational/physical therapy), and c) technological elements (amount of time alone in an isolette) during the first thirty days of hospitalization. Although this information can provide a comprehensive overview of the interaction experiences over infant's stay, addressing the research questions posed in this manuscript required the data to be examined at a much more granular level. To achieve this, a series of daily representations were constructed for each infant, containing 13 distinct attributes for each of their first 30 days post-admission. A complete listing of these attributes can be found in Table 2.

When viewed together, these attributes create a snapshot of an infant's experiences each day. Some are used to capture environmental stimuli in the use of an isolette, high frequency oscillatory ventilation (HFOV), conventional ventilation, or continuous positive airway pressure (CPAP) anytime over the prior 24 h, whereas others are used to quantify the broad range of interactions experienced by an infant each day. These interactions can include specific events, such as parental skin-to-skin care or occupational/physical therapy sessions, and the latency between their prior occurrences. As well as broader aspects of nursing care, including the count of new nurses encountered, a count of nurses with whom the infant had interacted before, the total interactions with all nurses, and the mean day count since the prior assignment of each repeat nurses to that particular infant. Finally, interaction events were aggregated into a derived estimate for total minutes of daily interaction, with nursing interactions estimated at 25 min each, skin-to-skin episodes at 60 min, and therapy session duration taken as logged from the EMR.

2.3. Social behavior data

Social behavior data were collected at approximately two years of age through the Brief Infant-Toddler Social and Emotional Assessment (BITSEA) [19,22]. The BITSEA is a standardized 42-item parent self-report questionnaire. It is used to evaluate social-emotional development, and as a first or second stage-screening tool for possible delays in social-emotional competence.

In particular, the BITSEA instrument contains three subscales with items specifically relevant to our hypothesis: Dysregulation, Social Competence, and Autism Spectrum Disorder. The Dysregulation subscale contains eight items ranging from sleeping and eating problems, to emotional reactions, sensory sensitivity, and regulatory capacity. The Social Competence subscale contains 11 items that assess capability in social-relatedness such as looking at a parent when their name is called,

Table 1
Demographic characteristics of extremely preterm infants in the study who were in high scoring or low scoring groups for each of the three subscales (Dysregulation, Social Competence, and ASD) on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA).

	Dysregulation Score		Social Competence Score		ASD Score	
	High Group n = 17	Low Group n = 13	High Group n = 20	Low Group n = 17	High Group n = 16	Low Group n = 17
Birthweight (grams)	728.6 ± 153.4	822.1 ± 233.9	787.3 ± 188.9	744.7 ± 171.6	792.3 ± 161.8	762.7 ± 177.5
Gestational age (weeks)	24.8 ± 1.0	25.4 ± 1.3	25.1 ± 1.2	24.6 ± 1.0	25.1 ± 0.8	25.3 ± 1.1
Gender						
Male	64.7%	61.5%	65%	64.7%	75%	64.7%
Female	35.3%	38.5%	35%	35.3%	25%	35.3%
Race						
White	47.1%	61.5%	60%	47.1%	56.2%	76.5%
Black	25.5%	38.5%	35%	29.4%	18.8%	23.5%
Hispanic	17.7%	0%	0%	11.8%	12.5%	0%
Other	9.7%	0%	5%	11.7%	12.5%	0%
Length of stay (days)	143.4 ± 41.7	96.5 ± 30.9	106.5 ± 31.0	129.2 ± 49.8	127.6 ± 47.2	104.6 ± 31.4
Parental marital status						
Married	35.3%	30.8%	35%	29.4%	18.8%	47.1%
Unmarried	64.7%	69.2%	65%	70.6%	81.3%	52.9%
Maternal education						
High school or below	41.18%	30.77%	40%	41.2%	43.8%	35.3%
College and above	58.8%	69.2%	60%	58.8%	56.3%	64.7%

trying to help when someone is hurt, pointing in an effort to show something far away, and following simple rules. The Autism Spectrum Disorder subscale contains 17 items that highlight typical behaviors that are commonly associated with ASD. These include not reacting when they are hurt, not hugging or feeding dolls or stuffed animals, spacing out, and avoiding physical contact.

For each subscale, designated cut-scores indicate areas of possible deficit/delay or possible problem. The intent of this study, however, was to explore relationships between early human interaction patterns and later social competence behaviors, regardless of their diagnostic value. Extremely premature infants often display elevated, but subclinical symptoms of social competence issues that affect functional behavior [23], leading to the emerging notion that there is an actual preterm behavioral phenotype. Consequently, upper and lower quartiles of scores were used to elicit behavioral profiles.

3. Analytical methods

Upon examination of the daily treatment of infants hospitalized in the NICU we found, despite limited mobility, that their network of social and environmental interactions could be quite complex. As a result, quantifying the relationship of these interactions to neurodevelopmental outcomes required a multi-faceted approach to investigating infant care. Broadly, the analyses presented throughout this manuscript were broken down into three components. First, we identified the pattern of item responses exhibited by our cohort and calculated subscale scores. Next, we performed univariate distributional and correlation analyses to identify important emergent associations among daily human interactions experienced by High and Low scoring infants. Finally, we micro-analyzed subcomponents of select attributes to elicit a finer understanding of higher-order interactions that took place between multiple elements of care.

3.1. Identification of item response patterns

The first analytical component focused on the distribution of responses for each individual item within the three BITSEA subscales of interest: Dysregulation, Social Competence, and ASD. Response patterns were identified and subscale scores were calculated. Based on the distribution of each subscale score, infants were divided into High and Low categories, resulting in 6 total groups. For each, the High category represented those infants scoring greater-than or equal-to the 75th percentile, while the Low category represented those scoring less-than or equal-to the 25th percentile.

After partitioning, 17 infants (34%) were classified as “High Dysregulation” and 13 infants (26%) as “Low Dysregulation”; 17 infants (34%) were classified as “Low Social Competence” and 20 infants (40%) as “High Social Competence”; and 16 infants (32%) were classified as “High ASD” and 17 infants (34%) as “Low ASD”. Of the infants in these categories, 7 infants (14%) were consistent across all three categories.

3.2. Univariate analysis – quantifying dimensions of care in relation to subscale outcomes

The next component focused on the day to day variability (intervariability) of daily care and interaction measures for each infant, with respect to their performance on the three chosen BITSEA subscales. Utilizing the daily representations detailed prior, we performed a distributional analysis comparing the mean value of infants' 30 daily feature vectors across each of the 13 attributes of care for those in the High and Low performance groups of each subscale.

For continuous variables, such as interaction minutes, the mean was calculated directly across the 30 daily feature vectors. While categorical indicators, such as placement in an isolette, required a transformation into a binary representation (0/1) of use on the respective day. As the number of days was standard for all infants, this transformation allowed the mean value to be computed where values closer to 1 represented more frequent use.

3.3. Univariate analysis – correlation of dimensions of care to subscale outcomes

Next, in an effort to further explore the direction and magnitude of the relation between each interaction attribute and subscale performance we look to a correlational analysis. To do so, the Low and High category infants were combined into a single group for each of the three subscales. For each subscale, a correlation coefficient was computed against the infants' mean interaction measure, computed as before, and their associated outcome scores.

3.4. Univariate analysis – primary nursing

Our last univariate analysis focused on deviations in developmental

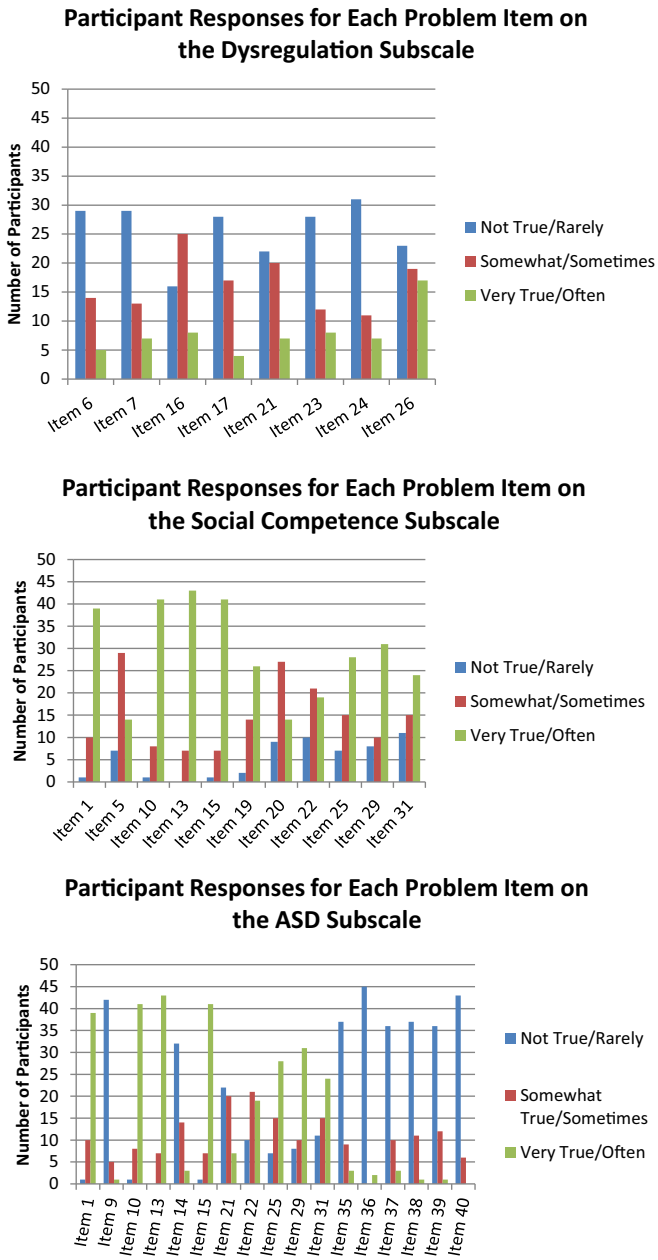

Fig. 1. Graphs showing participants' responses to problem items on the Dysregulation, Social Competence, and ASD subscales of the BITSEA instrument.

scores with respect to the patterns of care associated with the concept of primary nursing. For each infant, patient-based 1-mode nursing handoffs were used to count the number of shifts each nurse completed for an infant over their first 30 days of hospitalization. 1-mode handoffs represent each time one nurse completed a shift and handed off her patient to a nurse on the next shift [24]. For each infant, the percentage of total shifts was computed for each nurse, and compared between the High and Low categories of each subscale measure.

3.5. Higher-order interactions – environmental analysis

The final component of our investigation focused on capturing higher-order interactions along specific aspects of nursing care and technology utilization and their relation to Dysregulation, Social competence, and ASD outcome scores.

We first looked to the variability in an infant's environment. For the population of extremely premature infants being evaluated, an infant could be located within an isolette, or open-crib, and could utilize ventilatory technologies, including conventional ventilation, HFOV, or CPAP. In total these conditions represented six distinct combinations (henceforth referred to as states) of environment and ventilatory assistance. The state of the infant was assessed for each day, compared between High and Low scoring infants for each subscale.

3.6. Higher order interactions – extending interactions through the StickWRLD framework

As an extension, we performed an exploratory analysis using StickWRLD [3], a visual analytical program designed to help researchers identify significant correlations among groups of variables that are often statistically non-significant as individual entities. The goal of the exploration was to understand if there were combinations of human interactions that were associated with social competence outcomes and how they were associated.

3.7. Statistical analysis

With roughly 15-20 infants in the High and Low groups for each subscale, assessing the normality of the underlying distribution has been shown to be unreliable [26,27]. As this precluded the use of a standard parametric statistics, statistical significance when comparing means in the distributional and primary nursing analyses was determined using the Kruskal–Wallis test [28,29], a non-parametric one-way analysis of variance. Similarity, a non-parametric correlation measure was utilized in the Spearman's rank correlation coefficient [30,31].

In order to quantitatively compare the higher-order state differences in environmental state between infants in the High and Low subscale categories, first a normalized vector was constructed for each infant to represent the percent of time spent in each of the six states over their first thirty days. Next, utilizing cosine similarity, the pair-wise similarity was computed between environment vectors of each infant. The similarity results were then broken into two groups, representing "within-" (similarity between Low-Low category, and High-High category infants), and "between-" (similarity between Low-High category infants). A Kruskal–Wallis test was then performed on the within and between groups, capturing if the environmental state was more similar to infants in the same score category, or if no difference was observed based on the subscale score.

For the extension analysis, human interaction elements were binned and loaded into the StickWRLD visual framework per published protocol [25] and analyzed for two-node associative patterns at initial high residual values. Residual values were systematically decreased until the model reached a threshold corresponding to visual associative overload.

4. Results

The overarching goals of this study were to a) identify possible associations between human interaction with extremely premature infants in the NICU and later social competence outcomes and b) place emphasis on the social-emotional aspects of care that are often overlooked in intervention research. As such, we report significant differences between the High and Low performing infants in each subscale score at three confidence levels, 99%, 95%, and 90%. Although many works highlight only those items that fall below the common 0.05 threshold, we feel this is insufficient to aid in furthering research into the care patterns assessed by this study. With population groupings ranging from 15 to 20 infants we feel the reporting significance at three different confidence levels helps to provide a set of promising next steps for larger studies based on the results of this pilot. This is in line with the recent work by Greenland et al. [32], which supports the notion

Table 2
Univariate analysis of daily snapshot mean values and standard deviations [mean (SD)] of care dimensions of human interaction with extremely preterm infants in the NICU and later outcomes on the Dysregulation, Social Competence, and ASD scores on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA).

	Dysregulation Score		p-Value	Social Competence Score		p-Value	ASD Score		p-Value
	High Group	Low Group		High Group	Low Group		High Group	Low Group	
New nurses	1.18 (0.19)	1.25 (0.17)	0.49	1.22 (0.11)	0.20 (0.05)	0.82	1.21 (0.15)	1.24 (0.16)	0.77
Repeat nurses	1.56 (0.14)	1.63 (0.18)	0.19	1.63 (0.15)	1.56 (0.13)	0.12	1.56 (0.18)	1.61 (0.17)	0.21
Total nursing interactions	6.64 (0.91)	7.01 (0.74)	0.23	6.8 (0.70)	6.65 (0.85)	0.64	7.03 (0.61)	6.8 (0.70)	0.39
Average days since the last care by repeat nurses	2.38 (0.36)	2.21 (0.59)	0.52	2.25 (0.59)	2.23 (0.46)	0.88	2.19 (0.46)	2.29 (0.58)	0.52
Skin-to-skin care %	0.23 (0.18)	0.41 (0.19)	0.02**	0.39 (0.20)	0.18 (0.17)	0.003**	0.19 (0.17)	0.40 (0.18)	0.002**
Number of days since the last skin-to-skin care session	4.44 (2.46)	2.67 (1.59)	0.02**	2.71 (1.38)	4.66 (2.5)	0.004**	5.16 (3.63)	2.66 (1.41)	0.009**
Occupational/physical therapy session	0.02 (0.05)	0.03 (0.04)	0.60	0.04 (0.05)	0.02 (0.05)	0.25	0.02 (0.05)	0.029 (0.05)	0.56
Number of days since the last occupational/ physical therapy session	15.87 (9.33)	14.80 (7.97)	0.92	10.45 (3.87)	13.09 (9.67)	0.82	12.44 (7.99)	13.95 (7.87)	0.67
In isolette %	0.99 (0.03)	0.95 (0.16)	0.75	0.96 (0.13)	0.86 (0.33)	0.41	0.87 (0.34)	0.96 (0.14)	0.79
Conventional ventilation %	0.69 (0.33)	0.43 (0.42)	0.09*	0.43 (0.39)	0.59 (0.35)	0.18	0.57 (0.36)	0.42 (0.41)	0.22
HFOV %	0.04 (0.10)	0.02 (0.06)	0.42	0.01 (0.04)	0.03 (0.09)	0.46	0.04 (0.10)	0.01 (0.05)	0.47
CPAP %	0.22 (0.30)	0.47 (0.38)	0.06*	0.49 (0.37)	0.23 (0.29)	0.02**	0.29 (0.34)	0.45 (0.39)	0.28
Total interaction minutes	180.255 (22.23)	200.38 (19.99)	0.03**	195.46 (20.14)	177.63 (22.46)	0.01**	187.59 (20.36)	195.67 (17.91)	0.249

* Denotes significant p-values < 0.10.
** Denotes significant p-values < 0.05.

Table 3
Correlation table.

	Dysregulation Score	Social Competence Score	ASD Score
New nurses	−0.205 (0.278)	0.094 (0.579)	−0.038 (0.832)
Repeat nurses	−0.154 (0.417)	0.166 (0.327)	−0.264 (0.137)
Total nursing interactions	−0.368 (0.046**)	0.027 (0.875)	0.164 (0.361)
Average days since last care	0.080 (0.675)	−0.059 (0.730)	−0.099 (0.582)
SSC days	−0.257 (0.170)	0.371 (0.024**)	−0.373 (0.032**)
OTPT days	−0.088 (0.642)	0.056 (0.742)	−0.063 (0.726)
Isolette days	0.088 (0.645)	0.120 (0.479)	−0.051 (0.779)
Conventional ventilation days	0.431 (0.018**)	−0.319 (0.054*)	0.323 (0.067*)
CPAP ventilation days	−0.430 (0.018**)	0.415 (0.011**)	−0.211 (0.239)
HFOV days	0.149 (0.433)	−0.096 (0.573)	0.111 (0.540)
Interaction minutes	−0.432 (0.017**)	0.263 (0.116)	−0.048 (0.792)

Correlations (p-values) between care dimensions and subscale scores on the BITSEA.
* $p \leq 0.10$.
** $p \leq 0.05$.

Table 4
t-test between "High" and "Low" groups of primary care nursing (analyzed through patient-based 1-mode handoffs) and the Dysregulation, Social Competence, and ASD scores on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA).

		Mean (SD)	t Statistic	p-Value
Dysregulation	High Group	0.008 (0.002)	7.98	0.005**
	Low Group	0.01 (0.003)		
Social competence	High Group	0.009 (0.003)	1.682	0.195
	Low Group	0.01 (0.003)		
ASD	High Group	0.009 (0.003)	1.074	0.3
	Low Group	0.009 (0.003)		

** Denotes significance at the p < 0.01 level.

that lower p-values are themselves not more or less correct, only different in their confidence that the distributions truly differ. Consequently, while we highlight and discuss items found significant at these threshold values as highly promising next steps, all analysis results provide the computed p-values for each care attribute, allowing readers to interpret for themselves when designing future studies.

4.1. Item response patterns for each subscale

A total of 50 extremely preterm infants were included in the study. Gestational ages ranged from 22 5/7 to 26 6/7 weeks with an overall median age of 25 weeks. Group demographics were representative of the total NICU population and did not differ significantly in birthweight, gestational age, gender, or race. Summary statistics of demographic information are presented in Table 1.

Fig. 1 displays participant responses to each item on each of the three subscales of interest: Dysregulation, Social Competence, and ASD. Responses to the items on the Dysregulation subscale indicated that over half of the extremely preterm toddlers wouldn't touch some objects because of how they felt (67%), had trouble adjusting to changes (55%), and would often refuse to eat (73%). Toddlers were not prone to a) waking up at night and needing help to fall asleep, b) getting very upset, or c) gagging/choking on food. For the Social Competence subscale, responses indicated that the majority of toddlers in our cohort were affectionate with loved ones (98%) and were able to look at their parent when they were upset (98%) or their name was called (100%). However, some parents reported their toddlers as ***"sometimes" or "rarely"*** playing well with other children (33%), helping when someone was hurt (63%), or hugging/feeding dolls or stuffed animals (53%). Responses were also mixed for their toddlers' abilities to pay attention for a long time.

For the ASD subscale, high percentages of parents responded ***"Very True/Often"*** to the subscale items addressing joint attention, positive emotional display, and affection. Parents responded ***"Not True/Rarely"*** to items eliciting repetitive behaviors such as "putting things in a

Fig. 2. Row A presents heatmaps depicting the average percent of time spent in each environmental state for the High and Low infants of each subscale. Darker colors equate to higher values. **Row B** presents the granular view. Each line represents a single infant, highlighting the percent of time per state across the respective subscales.

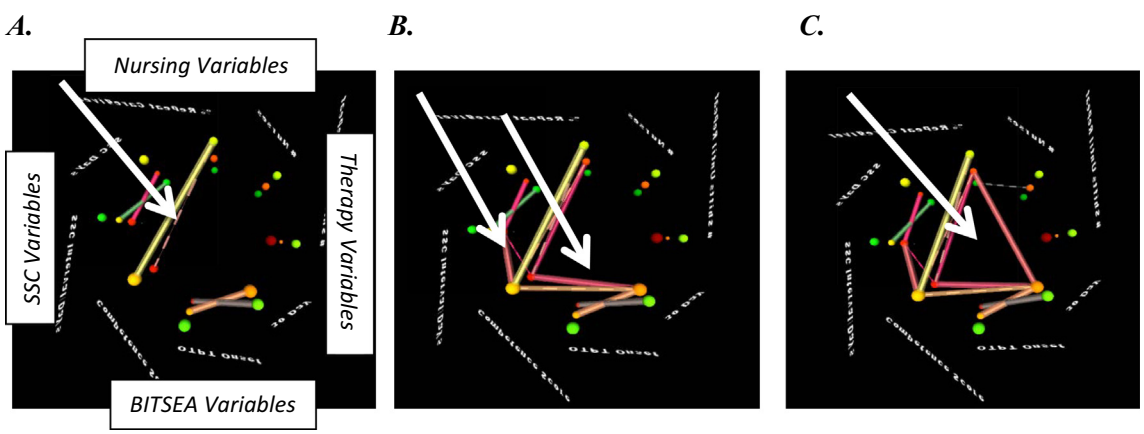

Fig. 3. StickWRLD Analysis – Each ball represents a data bin. Each line represents a significant correlation between data bins with stronger correlations represented by lines that are thicker in diameter. Colors are non-significant and are only used to aid in visual analysis. Arrows are used to highlight the significant associations described below. Additional associations that can be viewed are within-category associations (e.g., Total Amount of PT/OT and Amount of PT/OT in the First Thirty Days) and are consequently not emphasized.

SIGNIFICANT ASSOCIATIONS - Box A*: First Part of the Triangle -** Significant association between Percentage of Primary Caregiving and Social Competence scores ($p < 0.05$) ***Box B*: Two Findings: SSC Association and Second Part of the Triangle –** Significant association between Frequent SSC and Social Competence Score ($p < 0.05$) **and** significant association between Early Initiation of PT/OT (< 30 days of admission to NCH) and Social Competence scores ($p < 0.05$) ***Box C*: Third Part of the Triangle:** Significant association between Percentage of Primary Caregiving and Early Initiation of PT/OT ($p < 0.01$). ***This creates a statistically significant triangular relationship among Percentage of Repeat Caregivers, Early Initiation of PT/OT, and Social Competence scores.

special order over and over" (80%); repeating the same action or phrase over and over (74%), and repeating body movements over and over (90%). Parents did report an *absence or low observation* of behaviors on three subscale problem items designated by the BITSEA instrument as *possibly* being associated with ASD. (Item 21 – tries to help when someone is hurt; Item 25 – imitates playful sounds when asked; and Item 31 – hugs or feeds dolls or stuffed animals).

4.2. Univariate analyses – quantifying dimensions of care in relation to subscale outcomes

The results of the univariate statistical analysis for each of the 13 dimensions of care, broken down by outcome measure, are shown in Table 2. With regard to the Dysregulation outcome, we found an association to the daily amount of SSC and latency between SSC sessions. In particular, that higher amounts of SSC at shorter latency periods were significantly associated with lower Dysregulation scores. Moving next to the Social Competence outcome, shorter latency between SSC sessions, and an increased total daily amount of interaction minutes were both significantly associated with higher competency scores. Finally, an increased latency between SSC sessions was significantly associated with higher ASD scores.

4.3. Univariate analysis – correlation of dimensions of care to subscale outcomes

In a similar fashion, correlation analyses were broken down by subscale (Table 3). For the Dysregulation score, significant inverse

correlations were found between the daily total number of nursing interactions, combined human interaction minutes, and CPAP ventilation exposure, meaning that lower average amounts of interaction were associated with higher, dysregulation outcome scores and conversely higher averages with lower dysregulation scores. While, for the Social Competence outcome, significant positive correlations were found between the daily amount of SSC and CPAP ventilation exposure; indicating infants with higher percentage of days with SSC or CPAP usage tended to have higher competency scores, and vice-versa. Finally, with respect to the ASD outcome, we find significant positive correlations between the total daily amount of SSC and conventional ventilation exposure.

4.4. Univariate analysis – primary nursing

Rounding out the univariate analyses, we turned to the micro-analysis of the average percentage of shifts for each nurse for each patient (primary care percentage) (Table 4). We note a statistically significant association with the Dysregulation score but not with the Social Competence or ASD Scores.

4.5. Higher-order interactions – environmental analysis

Expanding our view of NICU experiences, our initial higher-order analysis focused on the technological aspects of the infant's environment. An aggregated view of the daily state across all infants in each group broken down by outcome score can be found in Table 3. We find a significant positive association between high Dysregulation and ASD outcome scores and days in an isolette with conventional ventilation ($p < 0.0001$; $p = 0.02$). Further, lower Social Competence scores were significantly associated with days in an isolette with CPAP ventilation ($p < 0.001$). A visual representation of these findings can be seen in Fig. 2. Fig. 2, Section A presents a series of heatmaps of the average percent of time spent in each environmental state for infants in the High and Low performance groups of each subscore. Fig. 2, Section B provides a more granular view, plotting the percent of time per state for each individual infant in each of the respective categories.

4.6. Higher-order interactions – extending interactions through the StickWRLD framework

Utilizing the StickWRLD framework, the final exploratory analysis looked to the network of human interaction (nursing care, parental SSC, and occupational/physical therapy sessions) over the infants first 30 days of hospitalization in relation to their Social Competence Score. As would be expected, the positive relationship between SSC and social competence noted in the univariate analyses was recognized. However, the ability of the StickWRLD framework to model complex relations allowed for the identification of a novel triangular association between the primary care percentage, the presence of occupational/physical therapy within the first 30 days of hospitalization, and the Social Competence score on the BITSEA. A visualization of the StickWRLD interaction structure can be found in Fig. 3.

5. Discussion

Our study found that extremely preterm infants spend an inordinate amount of time alone (80%) during their hospitalization in the neonatal intensive care unit. Essentially, 19 h a day, the infant's primary developmental environment is provided by non-human technology (i.e., incubator, monitor wires, ventilation devices) with the remaining hours consumed mostly with clinical interactions. There are physiological and psychopathological consequences to human isolation. Bowlby [33] and Bakwin [34] recognized over 70 years ago that early psychosocial deprivation had a negative impact on infant growth and development. Infants who experienced care in a hospital environment (i.e., sterile, lack of nurturing) had higher mortality rates, low weight gain, and disordered attachment behaviors. Thirty years later, the Early Bucharest Intervention Project, also noticed this trend in orphanages [35]. Researchers observed that children from Romania, who experienced institutional care as infants (e.g., task-oriented, non-responsive, non-nurturing) were more apt to display attachment disorders, anxiety, attention-deficit disorders, and behaviors similar to autism.

Emerging research has also implicated human isolation in altering the underlying physiology of regulatory mechanisms. Kumsta et al. [36] followed adoptees from Romanian orphanages and discovered that their hypothalamic-pituitary-adrenal (HPA) axes were disrupted even twenty years after their early adverse life event. The HPA axis, a hormonal response system to stress, is affected by early life stress as well as current stress experiences [37]. Extremely preterm infants in the NICU are at additional risk because they experience both conditions simultaneously. Studies have also revealed that the HPA axis may be especially vulnerable in infancy [38] and that early life stress events may alter the HPA axis to affect metabolic processes that impact energy management in the body [39].

Given these outcomes, it should come as little surprise that we found that toddlers who were born extremely premature exhibited lower dysregulation behaviors and higher social competence behaviors if they had more SSC, shorter latency periods between SSC sessions, higher incidences of primary nurse caregiving, and less time on conventional ventilation. It is probable that SSC and primary nurse caregiving mediate NICU isolation and foster more responsive caregiving that can help co-regulate the infant during an inherently stressful early life event. Co-regulation is fundamental and is possible with these infants. Skin-to-skin care has been shown to promote infant regulation [40,41] in addition to developmental care practices by medical staff [42]. Through the developmental care process, priority is placed on purposefully observing and interacting with infants and providing care based on what they are communicating. Infants who receive skin-to-skin care or developmental care have improved brain development and functional competence.

Our exploratory analysis hinted at the role of a combined human intervention system of primary nurses, parental engagement in SSC, and early therapy that may provide the co-regulatory piece that is often missing in traditional NICU care, but supported in the literature [42]. Further, our outcomes on the Dysregulation, Social Competence, and ASD subscales begin to paint a picture of the critical role that each human component plays in social development in the NICU. We also identified emerging relationships among the structure of nursing care, early therapeutic interventions, and social competence and we raise additional questions about the differential effects of ventilation on dysregulation and social competence.

It is highly encouraging that even though the amount of human interaction was limited, it did have impact and how it was structured made a difference. Our findings a) support the evidence that suggests that there may be early, targetable human interactional factors affecting later physiology and behavior and b) demonstrate that consistency of the human components within the NICU framework may be more crucial for development, rather than their mere existence or amount.

As we reflect on the results of our analyses, it is important to note the inherent limitations of this study, in particular the utilization of a retrospective cohort study and the fact that we were unable to assess the quality of interactions. Additionally, the retrospective nature precludes us from capturing data that has been known to affect neonatal neurodevelopment. However, our goal was to primarily capture the human interactional dimensions of the NICU and we feel that we have accomplished this comprehensively. Further, as is the case with all assessments and assessment protocols, the one-time administration of the BITSEA limits our ability to accurately assess behavior in that it cannot account for the presence of maturational effects that may occur over time. Finally, the population under study only included extremely

preterm infants who met the inclusion criteria of being born at a certain time in the NICU and also participated in a specific follow-up study that utilized the BITSEA assessment. We did not assess the association of the BITSEA outcomes with comorbidities, although in the primary study, the BITSEA outperformed the Pervasive Developmental Disorders Screening Test—II, Stage 2, Developmental Clinic Screener as it related to specificity, in the preterm sample [19].

6. Conclusion

In conclusion, parents, nurses, therapists, and the NICU physical surroundings each have defined, but interconnected roles in supporting regulation and social competence development in the extremely preterm infant population. An understanding of these roles can help us to broaden our view of neurodevelopment, and develop more systemic interventions that target the complete environmental system to eliminate human isolation in the NICU and improve infant regulatory and social competence capacities.

7. Future directions

This exploratory study raises many additional questions about the NICU human environment and how extremely preterm infants are impacted during their hospitalization. Further research is warranted in understanding how the infant's HPA axis is affected by NICU isolation and caregiving methods as well as investigating ways to increase high quality human interaction. Future prospective investigations should a) critically compare dysregulation, social competence, and ASD behaviors of extremely preterm infants and their term counterparts through school age, b) explore the differentiated effects of primary care nursing, early therapeutic intervention, and skin-to-skin care on later dysregulation and social competence behaviors, and c) identify ways to increase skin-to-skin care in the NICU.

Compliance with ethical standards

Funding

This study was not funded.

Conflicts of interest

All authors declare no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study where applicable and waiver of consent was granted for the actual retrospective study.

References

[1] H. Als, Toward a synactive theory of development: promise for the assessment and support of infant individuality, Infant Ment. Health. 3 (1982) 229–243.
[2] H. Als, S. Butler, S. Kosta, G. McAnulty, The Assessment of Preterm Infants' Behavior (APIB): furthering the understanding and measurement of neurodevelopmental competence in preterm and full-term infants, Ment. Retard. Dev. Disabil. Res. Rev. 11 (2005) 94–102.
[3] B. Westrup, Newborn Individualized Developmental Care and Assessment Program (NIDCAP) – family-centered developmentally supportive care, Early Hum. Dev. 83 (2007) 443–449.
[4] M. Coughlin, Transformative Nursing in the NICU: Trauma-informed, Age-appropriate Care, Springer, New York, 2014.
[5] M. Coughlin, Trauma-informed Care in the NICU: Evidence-based Practice Guidelines for Neonatal Clinicians, Springer, New York, 2017, pp. 3–12.
[6] S. Johnson, N. Marlow, Preterm birth and childhood psychiatric disorders, Pediatr. Res. 69 (2011) 11R-8R.
[7] K.C.K. Kuban, T.M. O'Shea, E.N. Allred, H. Tager-Flusberg, D.J. Goldstein, A. Leviton, Positive screening on the Modified-Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns, J. Pediatr. 154 (2009) 535–540.
[8] H.C. Glass, A.T. Costarino, S.A. Stayer, C. Brett, F. Cladis, P.J. Davis, Outcomes for extremely premature infants, Anesth. Analg. 120 (6) (2015) 1337–1351.
[9] P.T. Becker, J.E. Brazy, P.C. Grunwals, Behavioral state organization of very low birth weight infants: effects of developmental handling during caregiving, Infant Behav. Dev. 20 (1997) 503–514.
[10] J. Gonya, W.C. Ray, R.W. Rumpf, G. Brock, Investigating skin-to-skin care patterns with extremely preterm infants in the NICU and their effect on early cognitive and communication performance: a retrospectively cohort study, BMJ Open. 7 (2017) e012985 (Doi: 10.1136).
[11] R. Feldman, Z. Rosenthal, A.I. Eidelman, Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life, Biol. Psychiatry 75 (2014) 56–64.
[12] N. Charpak, R. Tessier, J.G. Ruiz, J.T. Hernandez, F. Uriza, et al., Twenty-year follow-up of kangaroo mother care versus traditional care, Pediatrics 139 (1) (2017) 2016–2063.
[13] R. Pineda, R. Guth, A. Herring, L. Reynolds, S. Oberle, J. Smith, Enhancing sensory experiences for very preterm infants in the NICU: an integrative review, J. Perinatol. 37 (2017) 323–332.
[14] M.J. Alvarez, D. Fernandez, J. Gomez-Salgado, D. Rodriguez-Gonzalez, M. Roson, S. Lapena, The effects of massage therapy in hospitalized preterm neonates: a systematic review, Int. J. Nurs. Stud. 69 (2017) 119–136.
[15] M. Herd, K. Whittingham, M. Sanders, P. Colditz, R.N. Boyd, Efficacy of preventative parenting interventions for parents of preterm infants on later child behavior: a systematic review and meta-analysis, Infant Ment. Health. J. 35 (2014) 630–641.
[16] M.G. Welch, M.R. Firestein, J. Austin, A.A. Hane, R.I. Stark, Family nurture intervention in the neonatal intensive care unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial, J. Child Psychol. Psychiatry 56 (11) (2015) 1202–1211.
[17] B.R. Vohr, L. Wright, A.M. Dusick, Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994, Pediatrics 105 (6) (2000) 1216–1226.
[18] C.J. Huppertz-Kessler, D. Verveur, J. Pöschl, To what degree does the NICU environment influence neurodevelopment of preterm infants? Klinische Padiatrie. 222 (4) (2010) 236–242.
[19] K.M. Boone, A.K. Brown, S.A. Keim, Screening accuracy of the Brief Infant Toddler Social-Emotional Assessment to identify autism spectrum disorder in toddlers born at less than 30 weeks's gestation, Child Psychiatry Hum. Dev. (2017), https://doi.org/10.1007/s10578-017-0768-2.
[20] C.A. Nankervis, E.M. Martin, M.L. Crane, K.S. Samson, S.E. Welty, L.D. Nelin, Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes, Acta Paediatr. 99 (2010) 188–193.
[21] E. Shepherd, T. Calver, E.M. Martin, J.C. Hitchner, S.E. Welty, L.D. Nelin, Outcomes of extremely premature infants admitted to a children's hospital depends on referring hospital, J. Neonatal Perinatal Med. 4 (2011) 45–53.
[22] M.J. Briggs-Gowan, A.S. Carter, Brief Infant-Toddler Social and Emotional Assessment (BITSEA) Examiner's Manual, Pearson, 2006.
[23] S. Johnson, N. Marlow, Preterm birth and childhood psychiatric disorders, Pediatr. Res. 69 (5) (2011) 11–18.
[24] J.E. Gray, D.A. Davis, D.M. Pursley, J.E. Smallcomb, A. Geva, N.V. Chawla, Network analysis of team structure in the neonatal intensive care unit, Pediatrics 125 (6) (2010) E1460–E1467.
[25] R.W. Rumpf, J. Gonya, W.C. Ray, Visual hypothesis and correlation discovery for precision medicine, AMIA Workshop on Visual Analytics in Healthcare Conference Paper, 2014.
[26] A. Ghasemi, S. Zahediasl, Normality tests for statistical analysis: a guide for non-statisticians, J. Pediatr. Endocrinol. Metab. 10 (2012) 486.
[27] D. Oztuna, A.H. Elhan, E. Tuccar, Investigation of four different normality tests in terms of type 1 error rate and power under different distributions, Turk. J. Med. Sci. 36 (2006) 171–176.
[28] W.H. Kruskal, W.A. Wallis, Use of ranks in one-criterion variance analysis, J. Am. Stat. Assoc. 47 (1952) 583–621 (and errata, ibid. 48 917-911).
[29] M. Hollander, D.A. Wolfe, Nonparametric Statistical Methods, John Wiley and Sons, New York, 1973, pp. 115–120.
[30] P. Sedgwick, Pearson's correlation coefficient, BMJ 345 (2012) E4483.
[31] C. Spearman, The proof and measurement of association between two things, Am. J. Psychol. 15 (1904) 72–101.
[32] S. Greenland, S. Senn, K. Rothman, J. Carlin, C. Poole, et al., Statistical tests, p values, confidence intervals, and power: a guide to misinterpretations, Eur. J. Epidemiol. 31 (2016) 337–350.
[33] J. Bowlby, World Health Organization, Maternal Care and Mental Health: A Report Prepared on Behalf of the World Health Organization as a Contribution to the United Nations Programme for the Welfare of Homeless Children / John Bowlby, second ed., (1952) Geneva.

[34] F. van der Horst, R. van der Veer, Loneliness in infancy: Harry Harlow, John Bowlby and issues of separation, Integr. Psychol. Behav. Sci. 42 (2008) 325–335.
[35] N.A. Fox, C.A. Nelson, C.H. Zeanah, The effects of psychosocial deprivation on attachment: lessons from the Bucharest Early Intervention Project, Psychodyn. Psychiatry. 45 (2017) 441–450.
[36] R. Kumsta, W. Schlotz, D. Golm, D. Moser, M. Kennedy, et al., HPA axis dysregulation in adult adoptees twenty years after severe institutional deprivation in childhood, Psychoneuroendocrinology 86 (2017) 196–202.
[37] M. Stephens, G. Wand, Stress and the HPA axis: role of glucocorticoids in alcohol dependence, Alcohol Res. 34 (4) (2012) 468–483.
[38] K.R. Kuhlman, I. Vargas, E. Geiss, N.L. Lopez-Duran, Age of trauma onset and HPA axis dysregulation among trauma-exposed youth, J. Trauma. Stress. 28 (2015) 572–579.
[39] J. Maniam, C. Antoniadis, M.J. Morris, Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes, Front. Endocrinol. 5 (2014) 1–17.
[40] R. Feldman, A. Weller, L. Sirota, A.I. Eidelman, Skin-to-skin contact (kangaroo care) promotes self-regulation in premature infants: sleep-wake cyclicity, arousal modulation, and sustained exploration, Dev. Psychol. 38 (2002) 194–207.
[41] R. Feldman, Z. Rosenthal, A.I. Eidelman, Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life, Biol. Psychiatry 75 (2014) 56–64.
[42] H. Als, G. B. McAnulty, The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) with kangaroo mother care (KMC): comprehensive care for preterm infants, Curr. Women's Health Rev. 7 (2011) 288–301.