Supporting and Enhancing NICU Sensory Experiences (SENSE)
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This study was registered on clinicaltrials.gov prior to enrollment under trial #201601057. This study was approved by the Washington University Human Research Protection Office with a Ceded Review at the University of Southern California. Parents signed informed consent.

Participants and study site. Seventy parent-infant dyads of very preterm infants born ≤ 32 weeks estimated gestational age (EGA) were recruited within the first week of life from consecutive admissions at St. Louis Children's Hospital NICU, an 85-bed (that expanded to 132-bed during the course of the study) level IV NICU from August 2017 to June 2018. Infants were excluded if they had a suspected or confirmed congenital anomaly, were assigned to the NICU's open ward (rather than a private room), or had parents who did not speak English. They were withdrawn if they became wards of the state or were transferred to a different NICU prior to discharge home.

Power. We defined primary outcome variables for each time point (at term equivalent age and one-year corrected age) and did a power analysis, to estimate sample size, incorporating both. The primary outcome variable at term equivalent age (35-41 weeks PMA) was the Excitability subscale score on the NICU Network Neurobehavioral Scale (NNNS). Excitability is a combination of both motor and behavioral responses, and previous work in our lab has demonstrated it to be a good predictor of later motor, cognitive and language outcomes. We estimated the variance of the Excitability subscore using data from preterm infants born < 30 weeks gestation enrolled in a longitudinal cohort from 2007-2010 and evaluated with the NNNS at term age. For this trial, a total sample of n=46 (23 in each group) will provide 80% power when the true NNNS group difference is 2.2 (2-sided test with alpha= 0.05). In a sample of typical full-term infants, the Excitability subscale score has a mean of 4.3 and a standard deviation of 2.4. A group difference of 2.2 would be a difference of almost 1 standard deviation. Our primary outcome variable at one-year corrected age was the Ages and Stages

Questionnaire (ASQ) Communication score. This was chosen as our primary outcome of interest, due to previous findings of poorer language outcomes in preterm infants hospitalized in low stimulation environments with poor parent engagement. The variance of the Communication score was estimated using a sample of preterm infants enrolled in our lab in 2011 who received the ASQ at age 3 years. A sample of n=46 provides 80% power when the true group mean ASQ difference is 9.5 (2-sided test with alpha= 0.05). In a normative sample, the Communication score on the ASQ has a mean of 52.9 with a standard deviation of 11.1. A total sample of n=46 (23 in each group) would be a large enough sample to detect a difference of less than 1 standard deviation across groups at the one-year follow-up assessment. Seventy infants were enrolled to account for 15% attrition during the course of the NICU hospitalization (for n=60 at term age) and another 20% attrition by the one-year follow-up assessment (n=48 at one-year of age).

Overview of procedures. Parent-infant dyads, enrolled within 7 days of birth, were randomized to either the standard-of-care group or SENSE multisensory program group. The randomization scheme was stratified on level of immaturity (≤ 28 weeks EGA or > 28 weeks EGA) and was uploaded to REDCap prior to study initiation. The biostatistician, who was not involved in other study procedures, established the randomization allocation sequence. Various members of the research team (research coordinator, principal investigator, neonatal therapist) enrolled families, pulling a sealed envelope that disclosed the group assignment after enrollment. Parents with infants in the SENSE group were provided with SENSE program education and daily support by a neonatal therapist to engage in the SENSE program (described below) in addition to receiving standard-of-care. Sensory exposures were tracked on bedside logs that contained sensory exposure dose targets for each day. The monitored standard-of-care

group received standard NICU care at the study site (described below) and tracked sensory exposures on bedside logs.

Standardized measures of maternal mental health and infant development were contained in a questionnaire that was completed by mothers at 35-41 weeks PMA in the NICU and at one-year corrected age. The questionnaire has been used in our longitudinal studies of preterm infants since 2007 and takes approximately 30 minutes to complete.

Standard-of-care. At the time of this study, much like other contemporary NICUs, parents were allowed to be present in the NICU 24 hours per day, with significant variability in the amount, types and timing of actual parent engagement. Infant holding was supported, provided the infant could maintain physiological and temperature stability. Infants were held while on mechanical ventilation, but holding was not encouraged when infants were on oscillatory ventilation and/or when chest tubes were in place. Nurses and therapists fostered parent participation through instruction on caregiving and developmentally appropriate interactions, but these were balanced with other priorities of medical care. No specific amount of positive sensory exposures was targeted, and practices varied based on the comfort level of nurses, the medical team, and the parents. Suboptimal parent presence, holding, and language exposure have previously been reported at the study site. The study site is consistent with other hospitals, where there is significant variation in use of sensory based interventions and decreased parental involvement. The SENSE program addresses the current lack of a national standard for positive sensory exposures and the resultant inconsistency of application of these exposures across hospitalization.

SENSE multisensory program. The SENSE program includes the provision of specific types and amounts of evidence-based tactile, auditory, visual, vestibular/kinesthetic, and olfactory interventions to be conducted by parents with their preterm infants, with a specific amount defined for each day of hospitalization (see Appendix 1). The program changes across PMA, and a sensory support team fills in the gaps when parents are not available**.** The education and parent guidance that is part of the SENSE program was overseen by a neonatal therapist (with the study using a neonatal occupational therapist and physical therapist).

SENSE program education. Parents randomized to the SENSE group received an educational booklet for the SENSE program which informed them about the premise of the multisensory interventions, along with identified targets in the amounts of daily multisensory exposures that are tailored to each infant's PMA. Parents could choose to provide one sensory exposure at a time or could provide multisensory interventions, based on the infant's tolerance. Parents were able to choose different types of each sensory exposure from options that have evidence to support their use and are appropriate at each PMA. The parents and medical team also opted for exposures within an infant's range of tolerance (such as using gentle human touch for an infant too sick to be transferred out of the bed to be held). Parents also received verbal education by the neonatal therapist on the research team within one week of enrollment and at least weekly thereafter to reinforce content in the booklet.

The sensory support team. When the parents or family members were unable to reach the target doses as defined in the SENSE program, a member of the sensory support team was assigned to deliver appropriate multisensory interventions. The sensory support team consisted of trained volunteers who provided gentle human touch and language exposure to medically stable infants as directed by the research team.

Modifications to the sensory intervention based on infant factors. The SENSE program is tailored to be responsive to each infant's cues when receiving the stimuli as

well as individualized based on concurrent medical issues. The neonatal therapist on the study team assessed the infant's tolerance each week, or more often if needed, and adjusted the multisensory interventions accordingly when not tolerated. The infant assessment used for the SENSE program is part of the manualized intervention and consists of infant observations, evaluation, and collaboration with the medical team. Any modifications to the structured dose and timing of the multisensory interventions were communicated to the parents, medical team, and sensory support team and documented by the research team.

Treatment fidelity/documenting sensory exposures. To assess treatment fidelity and to ensure treatment differentiation, sensory exposures (conducted by parents, the medical team, or the sensory support team) were captured on bedside logs for both groups. To ensure *treatment integrity,* we measured whether the daily doses defined in the SENSE program were being met each day, with specific attention to auditory and tactile exposures, which have large dose targets and are measurable by amount of time. Continuous review of sensory exposures during the course of the study also enabled activation of the sensory support team as needed. Differences in sensory exposure in the SENSE and standard-of-care groups are reported in a previous publication.

Masking participants and blinding evaluators. Parents were enrolled in this study, understanding that they would be assigned to one of two types of sensory approaches. They were masked from whether they were in the treatment group (SENSE program) or control group (standard-of-care), and the details of what we wanted them to do (within their assigned approach) were not communicated until after enrollment. All assessments in the NICU were conducted at the infant's bedside by a certified and trained evaluator, who was blinded to treatment assignment (as well as study details).

Medical factors. Medical factors were collected from both groups using the EPIC electronic medical record to define the characteristics of the sample and enable statistical control of other factors that can impact outcome. From these factors, a medical risk score was defined as the infant having any of these factors during the NICU hospitalization: inotropic support, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), parenteral nutrition > 21 days, mechanical ventilation > 7 days, bronchopulmonary dysplasia, or cerebral injury (grade III or IV intraventricular hemorrhage or cystic leukomalacia) due to evidence associating them with adverse neurodevelopmental outcome .

Social factors. Social factors were collected from EPIC as well as from the parent questionnaire. A social risk score, used in parallel research studies and modified for this study, was used to assess family environment after NICU discharge.

Outcomes at term equivalent age, prior to NICU discharge.

NICU Network Neurobehavioral Scale (NNNS). Between 35-41 weeks PMA, infants were assessed at bedside with the NNNS by a trained and certified evaluator blinded to treatment group. The NNNS has been used extensively with preterm infants, and has acceptable internal consistency (α =0.87-0.90), good test-retest reliability (α =0.30-0.44), and predictive validity with relationships to Bayley-II mental ($p=0.011$, $R^2=0.295$) and psychomotor ($p=0.002$, $R^2=0.441$) scores. It has also been shown to relate to ASQ scores at age 3 years. Habituation was not assessed, but the remaining 12 summary scores were used as outcomes.

Hammersmith Neonatal Neurological Evaluation. Between 35-41 weeks PMA infants were also assessed with the Hammersmith Neonatal Neurological Evaluation (HNNE). It has excellent clinical utility as a quick assessment of neonatal neurological status with acceptable content and criterion validity. The interrater reliability of the assessment is

good for both optimality scores and subtotal scores (ICC > 0.74 and ICC 0.6-0.74 respectively). The total score was used as an outcome variable.

Sensory processing. The questionnaire included the Sensory Profile 2 (short form). It is used in clinical practice and research and has good test-retest reliability (α=0.81-0.90), validity, and internal consistency (α =0.83). Summary scores for Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Auditory Filtering, Under Responsiveness/Seeks Sensation, Low Energy/Weak, and Visual/Auditory Sensitivity were used as outcomes.

Maternal mental health outcome. The questionnaire included the State Trait Anxiety Inventory (STAI), the Edinburgh Postnatal Depression Scale (EPDS), the Life Stress Subscale of the Parenting Stress Index (PSI), the Perinatal Post-Traumatic Stress Disorder Questionnaire (PPQ), the Parental Stressor Scale: NICU (PSS-NICU), the Maternal Confidence Questionnaire (MCQ), and the Infant Characteristics Questionnaire (ICQ). The STAI is the most widely used self-report assessment of anxiety in adults. Internal consistency coefficients range from 0.86-0.95, and test-retest reliability ranges from 0.65-0.89. The STAI has good construct and concurrent validity. The EPDS measures and has cut-offs for diagnosis of clinical depression. The EPDS has fair validity (specificity of 49-100%, sensitivity of 65%-100%, 83% predictive value). The scale has good test retest reliability of 0.92 , split half reliability of 0.88 with a standardized α coefficient of 0.87. The PSI (4th ed) screens for stress in the parent-child relationship and has good reliability, internal consistency with α=0.96 , and is useful across diverse populations. The PPQ is a measure of post-traumatic stress symptoms in the perinatal population and has good internal consistency (coefficient α=0.85) and test-retest reliability (r=0.92). The PSS NICU measures parental perception of stressors arising from the physical and psychosocial environment of the NICU and has acceptable internal consistency (Cronbach's alpha >0.7 for all scales) and good construct validity across all scales (r=0.45, p<0.05). The MCQ measures maternal confidence in

parenting and has fair test-retest reliability (0.69) and good internal consistency with Cronbach's alpha between 0.86 to 0.93. The ICQ measures perceptions about ability and competence in providing infant care and has good internal consistency (Cronbach's alpha from 0.39 to 0.79) and test-retest reliability (Pearson's r between 0.47 -0.70).

Outcomes at one-year corrected age.

Developmental outcome. At one-year corrected age, the parents completed the ASQ, a parent-report measure of developmental outcome, which can be used for children from 2 months to 5 years. Scores were obtained for: Communication, Gross Motor, Fine Motor, Problem Solving, and Personal-Social. The ASQ has good validity (combined validity 86%, 73%-100%) and reliability (test-retest reliability α =0.75-0.82, interrater reliability α =0.43-0.69) .

Sensory *processing:* Sensory processing was also measured at one-year corrected age using the Sensory Profile-2 (short form).

Maternal mental health. The STAI, PSI, modified PPQ, ICQ, and MCQ were also administered at 1-year corrected age. While the EPDS was used to determine maternal depression at term age, the Beck Depression Inventory II (BDI-II) was used to determine maternal depression at 1 year corrected age. The BDI-II has good validity, internal consistency with Cronbach's α coefficient 0.83 to 0.96 and good reliability (test retest r= 0.73 to 0.96).

Feeding outcomes at one-year of age. Feeding was assessed with the Pediatric Eating Assessment Tool (PediEat) and the Behavioral Pediatric Feeding Assessment Scale (BPFAS). The PediEAT measures symptoms of feeding problems in infants and children aged 6 months to 7 years. It has excellent internal consistency with Cronbach's α coefficient 0.83 to 0.92, good to excellent test-retest reliability (ICC=0.95), and established construct validity. The BPFAS defines patterns of mealtime and feeding

behaviors in young children aged 9 months to 7 years. It has good test-retest reliability (ICC=0.91), internal consistency with Cronbach's α coefficient 0.71 to 0.81, and established content and concurrent validity.

Statistical analysis.

Descriptive statistics were used to report characteristics of the sample. Differences in medical and sociodemographic factors across groups were explored using independent samples t-tests, chi-square analyses, regression models, and nonparametrics. All factors that were different across groups ($p<0.05$ and $r>0.30$) were considered for inclusion in the statistical model as a covariate, as long as they were not already represented in the social risk or medical risk scores.

First, mixed random effects models were used to investigate group differences in NNNS, ASQ, and other outcomes. Correlation between siblings, who are multiples, were modeled by using mother-infant dyad as a random effect. PMA at the time of assessment was controlled for due to its previously reported relation to neurobehavioral outcome. To further explore group differences, a second analysis was conducted, controlling for baseline covariates of social risk score and medical risk score. In addition, a final analysis was conducted to understand the potential impact of parent-driven, compared to sensory support driven, sensory interventions. An interaction between parent engagement (50% of interventions done by the parents) and treatment group was investigated in a factorial model. Other analyses of outcomes included mixed effects repeated measures ANOVA for continuous measures across time and using logistic regression for categorical outcomes of measures conducted at one point in time. The threshold of significance was $p=0.05$.