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Abnormal sensory reactivity in preterm infants during the first year correlates with adverse neurodevelopmental outcomes at 2 years of age

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Abstract

Background—Sensory experience is the basis for learning in infancy. In older children, abnormal sensory reactivity is associated with behavioural and developmental disorders. We hypothesised that in preterm infants, abnormal sensory reactivity during infancy would be associated with perinatal characteristics and correlate with 2-year neurodevelopmental outcomes.

Methods—We conducted a prospective observational study of infants with birth weight ≤1500 g using the Test of Sensory Function in Infants (TSFI) in the first year. Infants with gestational age ≤30 weeks were tested with the Bayley Scales of Infant and Toddler Development III (BSID III) at 24 months.

Results—Of the 72 participants evaluated at 4–12 months corrected age (median 8 months), 59 (82%) had a least one TSFI score concerning for abnormal sensory reactivity. Lower gestational age was associated with abnormal reactivity to deep pressure and vestibular stimulation ($p<0.001$). Poor ocular-motor control predicted worse cognitive and motor scores in early childhood (OR

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Contributors NLM designed the study, obtained grant funding, carried out preliminary analyses, participated in infant testing and data collection, reviewed and revised all drafts of the manuscript, and approved the final manuscript as submitted. ARS contributed to study interpretation, reviewed and revised all drafts of the manuscript, and approved the final manuscript as submitted. JS tested all infants with the TSFI, participated in data collection and entry, drafted the initial manuscript and approved the final manuscript as submitted. OC participated in data collection and analysis, drafted the revised manuscript and approved the final manuscript as submitted. JCS designed and executed the final statistical analyses and approved the final manuscript as submitted.

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16.7; p=0.004), but was tightly correlated to the presence of severe white matter injury. Poor adaptive motor function in response to tactile stimuli predicted worse BSID III motor (p=0.01) and language scores (p=0.04) at 2 years, even after adjusting for confounders.

Conclusions—Abnormal sensory reactivity is common in preterm infants; is associated with immaturity at birth, severe white matter injury and lower primary caregiver education; and predicts neurodevelopmental delays. Early identification of abnormal sensory reactivity of very preterm infants may promote parental support and education and may facilitate improved neurodevelopment.

Introduction

Prematurely born infants have a high risk of developmental and behavioural disorders compared with those born at term.[1–4] Because sensory experience is the basis for much of learning in infancy, sensory problems that affect preterm infants may contribute to their high incidence of later developmental disorders. Although hearing and vision impairments are well-documented sensory outcomes of prematurity, abnormalities in sensory processing (the organisation of sensation for use)[5] and sensory reactivity (an observable and immediate modulation of behaviour in response to a sensory stimulus)[6–8] are more difficult to identify and characterise.

Studies using parent-reported sensory profiles show that former preterm infants evaluated at 2 years of age demonstrate different patterns of response to their sensory environment compared with term counterparts, sometimes associated with worse neurodevelopmental scores.[9] These findings support the concept that sensory response patterns in infancy may contribute to a continuum of developmental and possibly behavioural disorders. However, these results are difficult to apply to clinical practice because the theoretical base of the assessment is complex and the testing and interpretation is designed for experts in occupational therapy and psychology.[10] We hypothesised that sensory reactivity may be a measurable clinical outcome for preterm infants and that early sensory reactivity abnormalities may be related to later neurodevelopmental disorders.

To test our hypothesis, we measured the responses of former preterm infants in the first year of life on a standardised sensory reactivity assessment. We investigated whether abnormal reactivity was associated with prespecified perinatal characteristics and whether adverse reactions to specific types of stimuli were correlated with 2-year neurodevelopmental outcomes.

Methods

We performed a prospective study of infants with birth weight ≤1500 g born between 05/2009 and 05/2011 and evaluated in the Neonatal Intensive Care Unit (NICU) Follow-Up Clinic at the Monroe Carell Junior Children's Hospital at Vanderbilt. We excluded infants with congenital brain abnormalities, genetic or metabolic disorders. The study was approved by the Institutional Review Board at Vanderbilt University, and written informed consent was obtained from parents of all participants.

Perinatal characteristics were extracted from the medical record. Gestational age (GA) was determined by the best obstetric estimate. Head ultrasound (US) or magnetic resonance imaging (MRI) results were available for all of the participants. Twelve participants had US and MRI scans, and three additional participants had only MRI results available. When MRI and US results were available, the MRI scan results were included into the analysis. All imaging was performed according to Vanderbilt approved neuroimaging protocols (see online supplementary materials) on resting, unsedated infants and all images were read by paediatric neuroradiologists. Severe white matter injury (severe WMI) was defined as the presence of grade III or IV intraventricular haemorrhage,[11] periventricular leukomalacia[12] or hydrocephalus on MRI or cranial US examination prior to discharge from the NICU. Primary caregiver education was obtained at the first clinic visit.

Participants were evaluated during one of their follow-up visits at 4–12 months corrected age using the Test of Sensory Function in Infants (TSFI)[13] and the Developmental Assessment of Young Children (DAYC)[14] cognitive, communication and motor domains as previously described.[15] For the analysis and results of the DAYC scores, see online supplementary material. Infants with GA ≤30 weeks were also evaluated at 24 months using the Bayley Scales of Infant and Toddler Development 3rd ed (BSID III).[16]

The composite scores for cognitive, motor and language domains were used as outcomes in this study. A single examiner trained by an experienced NICU occupational therapist with inter-rater reliability >90%, and masked to the infant's neonatal course, administered the TSFI. The TSFI testing was performed during the initial NICU follow-up clinic visit. The assessment was not attempted until the participant was in quiet and alert state in their caregiver's lap, and took 10 min on average. The test contains 28 items grouped into five categories: tactile deep pressure, adaptive motor function, visual-tactile integration, ocular-motor control and vestibular stimulation. Each domain represents processing within sensory modalities or between sensory and motor systems in response to an examiner-administered stimulus. Scores are classified as normal, at risk or deficient according to norm-referenced values for typically developing infants in four age categories. The score is determined based on whether the infant exhibits a simple behavioural reaction (eg, cry or grimace) or a physiological response (eg, nystagmus in response to a 360° spin).[13] Corrected age at testing was used to determine scoring categories.[17]

Hearing and vision impairments were recorded from routine ophthalmology and audiology assessments beginning in the NICU and followed to 2 years of age. Standard-of-care hearing assessment was auditory brainstem response (ABR) testing for all children performed by certified audiologists.[18] Standard ophthalmological exam was performed by board-certified paediatric ophthalmologists in a hospital clinic setting, and dilated retinal exam was only performed until complete vascularisation.[19] Minor vision impairments were defined as strabismus, amblyopia or myopia. Major vision impairments were defined as blindness, hemianopia and other types of cortical visual impairments. Minor hearing impairments were defined as partial or unilateral hearing loss, not requiring amplification. Major hearing impairments were defined as bilateral hearing loss requiring amplification. A severe motor impairment was defined as unilateral or bilateral cerebral palsy.

Statistical analysis

Continuous variables were summarised using medians and interquartile ranges, and categorical variables were summarised using percentages. TSFI scores were measured on an ordinal scale (deficient, at risk, normal). BSID composite cognitive, motor and language scores were used for all analyses. We used the proportional odds regression model to estimate the association of perinatal characteristics (gestational age, sex, primary caregiver education and severe WMI) with each of the TSFI domain. The proportional odds regression generalises logistic regression by allowing for more than two ordered categorical response levels. A proportional odds model estimates the association of a predictor with the odds of a more severe response while controlling for other covariates. Separate multivariable proportional odds models were fit for each of the TSFI domains, while including covariates for perinatal characteristics.

The Kruskal–Wallis test was used to determine whether TSFI risk categories were associated with BSID scores at 24 months in the subgroup of infants born at ≤30 weeks' GA. For these results, TSFI was the (categorical) predictor of interest rather than the outcome. Separate tests were done for each of the TSFI domains, and BSID scores (15 total tests) and adjustments for perinatal characteristics were also performed. All analyses were conducted with the R statistical program, V.2.15.3 (Vienna, Austria).

Population Characteristics

Parents of 72 of 79 (91%) eligible participants provided written informed consent.

Median corrected age at TSFI was 8 months (IQR=4.8–9.0). The majority of participants were male (58%) and 11 (15%) had severe WMI. Median GA of the participants was 28 (27,30) weeks. Results of Auditory Brainstem Response testing and eye examinations were available on all infants. Minor visual and hearing impairments affected 20.8% and 8.3% of participants, respectively; none had major impairments. For each infant, 55% of the primary caregivers (mother, father or grandparent) reported some education above high school.

Results

Sensory reactivity was abnormal in at least one of the five categories in 59/72 (82%) of infants, with responses to tactile deep pressure and vestibular stimulation most frequently affected (49% and 21% abnormal scores, respectively) (table 1).

Of the 56 infants with GA ≤30 weeks and thus eligible for routine 24-month assessments, 41 were evaluated using the BSID and 40 (73%) completed testing (table 2). One toddler unable to complete testing was subsequently diagnosed with an autism spectrum disorder. This child's prior TSFI scores were deficient in deep tactile and vestibular stimulation categories but normal in the other three. Five participants were diagnosed with cerebral palsy in early childhood. Of these, three had TSFI scores deficient in tactile deep pressure reactivity, one in adaptive motor and one in ocular-motor categories.

A comparison of participants controlling for sex, primary caregiver education and severe WMI showed that abnormalities in sensory modulation increased as GA decreased (table 3).

For every 1-week decrease in GA, infants were 1.68 times (95% CI 1.28 to 2.2) more likely to have a lower tactile deep pressure score (n=67; p<0.001). The probability of having abnormal reactivity to deep pressure was 17-fold greater for infants born at 23 weeks' GA than those born at 33 weeks. Reactivity to vestibular stimulation was more likely to be abnormal in infants whose primary caregiver had a high-school education or less, than in those whose primary caregiver reported more education (OR 5.1; p=0.02). Male sex correlated positively with odds of having abnormal reactivity to vestibular stimulation (OR 4.9; p=0.02). Severe WMI correlated with poor ocular-motor control (OR 16.7; p=0.004). The wide CI for this particular association was related to sparse data for some levels of WMI in ocular-motor control risk categories: 80% (4/5) of infants with deficient scores, 25% of at risk (1/4) and 11% (6/57) had severe WMI, which is reflected in the large odds ratio. However, the relatively small number of subjects in the deficient and at-risk categories leads to the large standard error. To verify that the wide CI was not an artefact of the regression model, we conducted additional sensitivity analyses where we adjusted for fewer covariates. All of these models gave very similar odds ratios and confidence intervals. Our data were therefore consistent with a potentially large effect of severe WMI, but with considerable uncertainty expressed in the wide CI.

Associations between abnormal sensory reactivity and 2-year neurodevelopmental outcomes (table 4)

Worse scores in adaptive motor function in infancy were predictive of poorer BSID motor scores (p=0.01) and language scores (p=0.04) at 24 months. Poor ocular-motor control in infancy was also associated with worse cognitive and motor scores (p<0.01 for both). No other abnormal reactivity scores were later associated with lower BSID scores. Again, after adjusting for all confounders such as severe WMI, associations with ocular-motor control lost significance. In contrast, associations between poor adaptive motor function and 24-month outcomes increased in significance (p<0.01).

We examined whether the total number of deficient categories was associated with BSID scores at 24 months. In separate linear regression models that controlled for severe WMI, gestational age, primary caregiver education and gender, we found no evidence that the total number of deficient categories was associated with cognitive scores (p=0.27), language scores (p=0.73) or motor score (p=0.13). For each of the outcomes, the direction of the association was identical with more total deficient categories associated with lower scores, but none of the associations reached statistical significance in adjusted models.

Discussion

We found that a brief sensory assessment performed in the NICU follow-up clinic provides objective data with clinical relevance and predictive value in a high-risk preterm infant population. Using this assessment, we showed that abnormal reactivity to sensory stimuli is associated with the same perinatal characteristics (immaturity, severe WMI, lower primary care-giver education) as adverse cognitive, motor and communication development. However, even after adjusting for these characteristics, abnormal sensory reactivity

independently increased the odds of having poor outcomes at 2 years. This is consistent with the importance of sensory experience in infant learning and development.

Most preterm infants in our study had abnormal sensory reactivity in at least one domain of the TSFI. The high frequency of abnormal sensory reactivity in our study is consistent with the findings of other recent studies using the Infant and Toddler Sensory Profile (ITSP), a parent-report questionnaire. These studies demonstrated markedly different patterns of response to their sensory environment in children born preterm compared with term counterparts.[9,20] A single study reported differences in late preterm infants (34–36 weeks) compared with full-term infants in all domains of the TSFI.[6] In that report, an increase in sensory modulation difficulties was correlated with lower GA and associated with decreased infant social participation and parental satisfaction.

Abnormal sensory reactivity can have important implications for the adjustment of parents and infants following NICU discharge, especially when manifested by an aversive reaction to a stimulus (termed sensory defensiveness), such as crying, grimacing or withdrawal. Along with prematurity, crying is one of the primary infant behaviours associated with a Shaken Baby Syndrome (SBS) episode, especially with onset in the first 4 months.[21,22] An early evaluation of sensory defensiveness in preterm infants may facilitate parent education and awareness of supportive developmental services, although not necessarily sensory integration therapies.[23]

We found that lower gestational age was associated with abnormal reactivity to deep pressure and vestibular stimulation. A potential explanation may relate to the altered sensory experiences inherent in the NICU hospitalisation of preterm infants, such as procedural tactile input, supine immobilisation and unopposed gravitational forces during critical windows of neurological development.[24–26] Premature transition from the protective and filtered intrauterine sensory environment may result in the construction of altered and maladaptive sensory representations.[27–29]

In our cohort, at-risk or deficient scores in the domain of ocular-motor control were associated with worse cognitive and motor scores in infancy and at 2 years, although this finding was confounded and possibly explained by the presence of severe WMI. The TSFI ocular-motor control domain assesses lateralisation of the eye and visual tracking ability in response to external stimuli. These responses depend on a widely distributed neural network that later contributes to executive function skills and cognitive and motor function.[30,31] This network is also highly dependent upon the integrity of the voluntary pathways in the frontal cortex and the basal ganglia as well as reflexive influences in the parietal and occipital cortex,[32–34] all of which are susceptible to preterm brain injury.[35] Therefore, preterm brain injury, through alterations of this network, may contribute to poor ocular-motor control in response to visual stimuli and subsequently lead to cognitive and motor delays. However, a larger cohort and a prespecified mediation analysis would be necessary to explore this finding.

Most concerning was the association we found between poor adaptive motor function in infancy and worse motor and language scores, which remained even after adjusting for all

confounders. The light touch used as the stimulation in the motor paradigm of the sensory assessment elicited an abnormally defensive response in 40% of our sample and supports the findings of others on altered tactile thresholds.[36] The adaptive motor response is dependent on thalamocortical relays modulating the connectivity between sensory and motor areas. Recent research has shown that these neural networks are affected by intensive care hospitalisation in preterm infants without severe WMI.[37] The potential for altered adaptive motor function may therefore be inherent to the altered neurodevelopment of preterm infants in the NICU.

The adaptive motor response to tactile stimuli is also an essential tool for learning in infancy[3839] and is the basis for future developmental processes. This has been demonstrated in school-aged children in whom a maladaptive response was associated with poor social-adaptive behaviours,[40] as well as sensory and motor confusion.[41] We propose that testing high-risk infants using the adaptive motor function elements of the TSFI might facilitate referral in infancy for needed rehabilitative services.

A strength of our study is the use of a relatively simple standardised assessment tool that can be administered by a variety of professionals and provides information relevant to clinical practice. Early infant experience and its effect on sensory processing has been an area of interest in neurodevelopmental research of high-risk infants, but few clinically applicable assessments are available.[23] Objective and quantitative sensory function assessment in infants are difficult to develop due to infants' limited ability to participate in the testing process for lengthy intervals, making brevity and a predominantly passive tool essential. Furthermore, the interpretation of the assessment tools must be rapid and simple in a paediatric outpatient setting, especially when specialists such as occupational therapists or psychologists are unavailable.

A limitation of the study is our use of TSFI since the test is performed in a clinic setting on a single occasion and may not represent the full capabilities of an infant compared with the home setting. The ITSP, a parent questionnaire, is an alternative tool. Although subjective, this test has the advantage of reporting sensory behaviours over a broader range of time and environmental settings. Another limitation is the loss to follow-up at 2 years. At the time of our study, infants >30 weeks' GA were not routinely followed in our clinic after 1 year. As a result, infants born between 31 and 33 weeks were not routinely seen at 24 months. These infants, 64% of whom had at least one abnormal TSFI score, are still at high risk for delays, and additional follow-up could have identified other areas of concern. Our NICU follow-up clinic now follows all infants born at ≤33 weeks to 36 months.

In conclusion, preterm infants often have abnormal sensory reactivity, worsened by immaturity and severe WMI. This reactivity is associated with concurrent delays in developmental milestone acquisition and poor neurodevelopmental outcomes in early childhood. Current theories of brain development hypothesise the presence of critical windows of brain development, during which atypical sensory exposure may establish long-term functional consequences.[242542] In this framework, the results of our study further support the need for objective, quantitative and infant-friendly research methodologies to understand the cortical processes involved in sensory modulation of preterm infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known on this topic

- Sensory experience is the basis for learning in infancy.
- Abnormal sensory reactivity in older children is associated with behavioural and developmental disorders.

What this study adds

- Abnormal sensory reactivity is common in preterm infants at 4–12 months corrected age and correlates with lower gestational age and severe white matter injury.
- Abnormal sensory reactivity in infancy is associated with abnormal neurodevelopment at 24 months corrected age.

Table 1

Population characteristics

	All infants (N=72)	Infants followed to 24 months (N=40)
Infant characteristics		
Male sex, n (%)	42 (58)	26 (65)
GA completed weeks, median (IQR)	28 (27 to 30)	28 (27 to 30)
Birth weight g, median (IQR)	1038 (815 to 1308)	1040 (775 to 1850)
Severe white matter injury, n (%)	11 (15)	4 (10)
Minor sensory impairments		
Visual, n (%)	15 (20.8)	11 (27.5)
Hearing, n (%)	6 (8.3)	2 (5)
Primary caregiver education, n (%)		
Unknown	1 (1)	2 (5)
Less than 12th grade	7 (10)	5 (12.5)
High-school graduation	24 (33)	11 (27.5)
Partial college or trade school	26 (36)	11 (27.5)
Graduated college	9 (12)	8 (20)
Graduate education	5 (7)	3 (7.5)

IQR (25%, 75th).
GA, gestational age.

Table 2
Sensory reactivity and developmental testing scores

Item	N	%
TSFI scores at 12 months	72	100
Infants deficient or at risk in specific category		
Adaptive motor function	29	40
Reactivity to tactile deep pressure	35	49
Visual-tactile integration	15	21
Ocular-motor control	8	12
Reactivity to vestibular stimulation	15	21
Number of abnormal categories per infant		
All normal	13	18
1 at risk or deficient category	22	30
2 at risk or deficient category	16	22
3 at risk or deficient category	13	18
4 at risk or deficient category	5	7
All abnormal	3	4
	N	Median (IQR)
BSID III scores at 24 months	40	
Cognitive		95 ((80 to 100)
Motor		95 ((82 to 104)
Language		91 ((79 to 97)

IQR (25%, 75th).

Table 3

Abnormal sensory reactivity as a function of gestational age at birth, primary caregiver education, sex and severe white matter injury

Perinatal characteristic	Tactile deep pressure	Adaptive motor function	Visual tactile integration	Ocular-motor control	Vestibular stimulation
GA (1 wk decrease)	1.68 (1.28 to 2.2)**	1.07 (0.87 to 1.31)	1.14 (0.88 to 1.49)	1.11 (0.76 to 1.62)	0.92 (0.69 to 1.22)
Sex (male)	1.55 (0.56 to 4.31)	1.6 (0.59 to 4.35)	1.11 (0.33 to 3.74)	0.14 (0.01 to 1.43)	4.9 (1.19 to 20.3)*
Severe WMI	0.33 (0.08 to 1.44)	1.99 (0.51 to 7.72)	1.35 (0.3 to 6.13)	16.91 (2.47 to 115.66)**	4.58 (0.82 to 25.48)
ED<HS	2.65 (0.97 to 7.24)	0.63 (0.23 to 1.72)	0.68 (0.21 to 2.2)	3.36 (0.54 to 20.91)	5.13 (1.28 to 20.5)*

Results expressed as OR (95% CI).

* p<0.01;

** p<0.001.

ED, primary caregiver education; GA, gestational age; HS, high school; severe WMI, severe white matter injury.

Arch Dis Child Fetal Neonatal Ed. Author manuscript; available in PMC 2016 March 08.

Table 4

Abnormal TSFI scores in infancy are associated with worse BSID III scores at 24 months

TSFI category	BSID III	Deficient median (IQR)	At-risk median (IQR)	Normal median (IQR)	p Value
AMF	Cognitive	90 (78 to 90)	91 (84 to 97)	98 (88 to 105)	0.17*
AMF	Language	71 (66 to 74)	94 (84 to 100)	96 (79 to 102)	0.04*
AMF	Motor	82 (70 to 84)	91 (84 to 97)	103 (93 to 112)	0.01*
OMC	Cognitive	65 (65 to 70)		95 (88 to 100)	<0.01†
OMC	Language	77 (71 to 79)		91 (81 to 98)	0.07†
OMC	Motor	58 (58 to 61)		100 (85 to 107)	<0.01†

IQR (25th, 75th).

*Kruskal–Wallis test.

†Wilcoxon test.

AMF, adaptive motor function; OMC, ocular-motor control.