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Auditory Neural Myelination is Associated with Early Childhood Language Development in Premature Infants

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Abstract

Background—Auditory neural myelination (ANM) as evaluated by auditory brainstem evoked response (ABR) during the neonatal period has been used as a surrogate outcome for long-term neurodevelopment. The validity of ANM as a surrogate outcome for long-term neurodevelopment has not been well studied.

Aim—Evaluate the association of ABR I-V interpeak latency (IPL), an index of ANM, at 35 weeks postmenstrual age (PMA) with language outcome at 3 years of age.

Design—Prospective study

Subjects—24–33 weeks gestational age (GA) infants were eligible if they did not meet exclusion criteria: craniofacial malformation, chromosomal disorders, deafness, auditory dys-synchrony, TORCH infection, or non-English speaking parents. Infants with malignancy, head injury, encephalopathy, meningitis, blindness, or who died or relocated were also excluded.

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Contributors list: Sanjiv Amin conceptualized the study and was responsible for the conduct of the study. Mark Orlando evaluated auditory neural myelination. Dawn Vogler-Elias performed language assessment. Hongyue Wang performed statistical analyses. All authors contributed towards writing the manuscript.

Declaration of competing interest: None

Conflict of Interest:

None of the authors have any financial or personal relationship with other people or organizations that could inappropriately bias the work.

Outcome Measures—ABRs were performed at 35 weeks PMA using 80 db nHL and I-V IPL (ms) measured. Auditory Comprehension (AC) and Expressive Communication (EC) were evaluated by a speech-language pathologist at 3 years of age using Preschool Language Scale.

Results—Eighty infants were studied. The mean GA and birth weight of infants were 29.2 weeks and 1336 g, respectively. There was association of worse ear I-V IPL and better ear I-V IPL with AC (Coefficient -5.4 , 95% CI: $-9.8 - -0.9$ and Coefficient -5.5 , 95% CI: $-10 - -0.9$, respectively) and EC (Coefficient -5.6 , 95% CI: $-9.5 - -1.8$ and Coefficient -6.7 , 95% CI: $-10.6 - -2.7$, respectively) after controlling for confounders.

Conclusion—The neonatal I-V IPL is a predictor of language development at 3 years of age in preterms.

Keywords

myelination; interpeak latency; nerve conduction velocity; neurodevelopment

INTRODUCTION

Premature infants are at increased risk for abnormal long-term neurodevelopmental outcome.(1) It is well accepted that exposure of immature brain to adverse events that lead to brain developmental disruption or injury during the critical period of perinatal brain development is primarily responsible for abnormal long-term development. The perinatal period of brain development is characterized by differentiation and maturation of oligodendroglia which is responsible for myelination, a neurodevelopmental process that peaks during this period.(2) Therefore, premature infants are vulnerable to abnormal brain myelination from developmental disruption or injury during the critical period of perinatal brain development. There is ample evidence to suggest that white matter injury or abnormal brain myelination during early human brain development lay the foundation for abnormal long-term neurodevelopmental outcome including language impairment.(3-5)

Although magnetic resonance imaging (MRI) is increasingly used to evaluate white matter injury, the use of MRI to evaluate brain myelination in premature infants before discharge from the Neonatal Intensive Care Unit (NICU) can be challenging and is often limited in prognostic and research value before term equivalent age (40 weeks gestational age) for long-term neurodevelopmental outcome.(6, 7) Because of temporal and regional emergence of myelination in the auditory pathway during the perinatal period, auditory neural myelination provides a window for evaluation of brain myelination.(8) Auditory neural myelination can be evaluated in premature infants before discharge from the NICU by auditory brainstem evoked response (ABR), a non-invasive objective tool, and is therefore increasingly used as a surrogate outcome for brain myelination and related neurodevelopmental outcomes.(9-12)

The ABR waveform in premature infants at 35 weeks post-menstrual age is comprised of 3 waves (I, III, and V).(12) The interpeak latencies (IPL, I-III, III-V, I-V), index of auditory neural myelination, reflect nerve conduction velocity at different levels of auditory pathway. (13-15) The central nerve conduction velocity between wave I and V is one of the most

important ABR measure of myelination and reflects the overall integrity of the peripheral auditory nervous system.(16) The decrease in IPL I-V or improvement in central nerve conduction velocity reflects overall improvement in auditory neural myelination. Although, auditory neural myelination is used as a surrogate outcome measure of brain myelination in neonatal clinical studies, the association between auditory neural myelination evaluated before discharge from the NICU and subsequent neurodevelopment in early childhood has not been well studied in premature infants.(17) Our objective was to evaluate the association between auditory neural myelination evaluated by ABR performed at 35 weeks PMA and subsequent language outcome at 3 years of age. The study was approved by the Institutional Human Subject Review Board. Parental consent was obtained for each subject enrolled in the study.

METHODS

Study Design

We performed a prospective longitudinal study to evaluate the association between auditory neural myelination evaluated at 35 weeks post-menstrual age (PMA) and later language outcome evaluated at 3 years of corrected age in premature infants 33 weeks gestational age (GA).

Subject Population

Infants 33 weeks GA admitted to the NICU were eligible at 35 weeks PMA unless they had craniofacial anomalies, chromosomal disorders, congenital hearing loss, auditory dys-synchrony, non-English speaking parents, or infection with cytomegalovirus, toxoplasmosis, rubella, herpes, and syphilis. In addition, infants with history of malignancy, head injury requiring rehospitalization, encephalopathy, meningitis, blindness, delayed onset hearing loss (conductive or sensori-neural), or who died or relocated to out of state before language assessment at 3 years of corrected age were excluded. Gestational age (GA) was assessed by obstetric history, or if obstetric history was unreliable, by Ballard examination.

Auditory Neural Myelination at 35 weeks Post-Menstrual Age

ABRs were recorded at 35 weeks PMA using a Biologic Navigator Evoked Response System with the subjects lying supine in the crib in a quiet room and skin temperature $> 35.5^{\circ}\text{C}$. We considered 35 weeks PMA to evaluate auditory neural myelination based on the previous report that the prognostic power of the ABR increases when the test is performed closer to discharge from the NICU.(18) In addition it may be difficult to measure IPL before 34 weeks PMA as ABR waveform is often incomplete because of age dependency of ABR maturation.(12, 19) Testing was performed by audiologists skilled in the administration of ABR tests. Electrode sites were mastoid (reference), midline on high forehead or crown of the head (active), and shoulder (ground). Electrode gel was applied to silver/silver chloride electrodes. Bilateral monaural ABR tests were performed using 80 dB nHL broadband click stimuli with insert earphones. The clicks were presented at a repetition rate of 29.9/sec, and three runs of 2000 repetitions were recorded for each ear. The 2 most replicable runs for each ear were averaged and used for analysis. The ABRs were analyzed by the audiologists without knowledge of infant's clinical characteristic. In addition, tympanometry using a

1000 Hz probe was performed at 35 weeks PMA in each subject to rule out middle ear disease. Transient otoacoustic emission tests were performed to rule out outer hair cell dysfunction at 35 weeks PMA. The IPL I-V (or central nerve conduction velocity) was the primary predictive ABR variable. For each individual subject, the ear with a shorter I-V IPL was defined as a better ear I-V IPL and conversely the ear with a longer I-V IPL was defined as a worse ear I-V IPL.

Language Evaluation at 3 years of Age

Language assessment on each subject was performed at 3 years of corrected age using validated and standardized Preschool Language Scale -4 (PLS-4) by a speech-language pathologist blinded to ABR findings and clinical characteristics. The PLS-4 is an individually administered scale for identifying language disorders and delays in children birth through 6 years old. The PLS-4 evaluates Auditory Comprehension (or receptive) and Expressive Communication language skills in the areas of attention, play, gesture, vocal development, social communication, vocabulary, concepts, language structure, integrative language skills, and phonological awareness. The Auditory Comprehension and Expressive Communication subtests are each based on a mean of 100 with a standard deviation of 15. The child's chronological age at time of the study visit was used to calculate standard scores and determine testing start item. Language testing took place at a child-size table in a quiet examination room with parents present depending on the child's comfort level. Auditory Comprehension and Expressive Communication language scores were obtained on each subject.

Clinical and Demographic Factors

Information on demographics and neonatal clinical characteristics before 35 weeks PMA and during the interval between 35 weeks PMA and 3 years of corrected age were prospectively collected for each individual subject. In addition, information on maternal education, marital status, and employment status at the time of language assessment at 3 years of corrected age was collected for individual subjects.

Respiratory distress syndrome was defined based on chest x-ray findings and need of surfactant. Intraventricular hemorrhage grading on head ultrasound findings was based on Papile's classification and was reported by the pediatric radiologist.⁽²⁰⁾ Cystic periventricular leukomalacia was defined and reported by the pediatric radiologist based on head ultrasound findings of echo lucent cysts in the white matter. Chronic lung disease was defined based on oxygen requirement at 36 weeks PMA. Necrotizing enterocolitis was defined based on x-ray findings of pneumatosis and/or free air in the peritoneum as reported by the pediatric radiologist.

Statistical Analyses

The analyses were performed using version 9.3 of the SAS System for Windows (SAS institute Inc., Cary, NC, USA). To evaluate the association between auditory neural myelination and language outcomes, multiple linear regression analyses were performed with the Expressive Communication language score or Auditory Comprehension language score as a dependent variable and I-V IPL as independent variable. Gestational age, maternal

education, maternal marital status, maternal employment status, race, ethnicity, gender, middle ear infections during the first 3 years, number of siblings, bilingual status, placement in a day care center or school, chronic lung disease, intraventricular hemorrhage, cystic periventricular leukomalacia, type of enteral feeding (breast milk or formula during neonatal stay), and participation in Reach Out and Read Program were considered potential confounders based on literature and included in regression models.(21-31) Collinearity diagnostics were performed using variance inflation factor and tolerance before being included in the regression model. Separate regression models were created for each language outcome: Auditory Comprehension and Expressive Communication language score. Both worse ear I-V IPL and better ear I-V IPL were independently evaluated as predictive variable for each language outcome in regression models. Thus, a total of four separate regression models were created to predict individual language outcome using each predictive variable separately. The clinical factors included in the final regression models were identified using best subset model selection with minimum Akaike's Information Criteria. We chose best subset model selection using Akaike's Information criteria because it provides an objective way of determining which model among a set of models is most parsimonious regardless of the order in which models are computed and it is founded on solid statistical principles, i.e. maximum likelihood. An alpha of 0.05 was considered statistically significant.

RESULTS

Ninety infants were enrolled in the study. Seven infants (5 infants relocated, 1 infant died, 1 infant was diagnosed with delayed hearing loss) were excluded. Three infants withdrew from the follow-up language assessment. Eighty infants met study criteria and completed follow-up language assessment at 3 years of corrected age.

Baseline Clinical Characteristics

The baseline demographic and clinical profile of study population before ABR evaluation at 35 weeks PMA is shown in Table 1. The mean birth weight and GA for the study population were 1336 g (standard deviation [SD] 449) and 29.2 weeks (SD 2.6), respectively. There were 43 males (53%), and 44 infants (55%) were delivered by cesarean section. Only one infant had a 5 minute Apgar score < 3. The study population was mostly Caucasian (n = 49, 61%) and non Hispanic (n = 69, 86%). The clinical profile of study population was characterized by prevalence of 68% (n = 55) respiratory distress syndrome, 4% (n=3) grade III-IV intraventricular hemorrhage, 4% (n=3) cystic periventricular leukomalacia, 30% (n =24) culture proven sepsis, and 3% (n=2) necrotizing enterocolitis (with pneumatosis or perforation). Majority of infants (80%) received breast milk during the NICU stay. All infants had unconjugated hyperbilirubinemia during the first 2 weeks after birth with a mean peak total serum bilirubin concentration of 9.1 (SD 2.1) mg/dL.

Neonatal Auditory Neural Myelination

None of the infants had middle ear disease or outer hair cell dysfunction as evaluated by tympanometry and otoacoustic emission test, respectively, at the time of auditory assessment. The mean and SD for worse ear I-V IPL was 6.41 ± 0.87 ms, while the mean

and SD for better ear IPL was 5.9 ± 0.83 ms. The mean difference between worse and better ear I-V IPL was 0.51 ms (range, 0 - 2.9 ms). Overall, 55% of better I-V IPL were from right ear (or conversely 45% of worse I-V IPL were from right ear) while 45% of better I-V IPL were from left ear (or conversely 55% of worse I-V IPL were from left ear). There was no significant correlation between I-V IPL and GA (or postnatal age). The correlation between GA (or postnatal age) and better ear I-V was -0.04 ($p = 0.7$) and the correlation between GA (or postnatal age) and worse ear I-V was 0.02 ($p = 0.4$).

Post-discharge Characteristics

The clinical profile of infants during the interval period between ABR evaluation at 35 weeks PMA and language assessment is shown in Table 2. During the interval period, 10 (12.5%) infants had chronic lung disease. At the time of language assessment, 33 (41%) infants had received early intervention, 24 (30%) infants were in day care or preschool and 7 (8.7%) infants had participated in Reach out and Read Program. At the time of language assessment, only one infant was bilingual and the mean (median) number of siblings were 1.4 (1.5). The mean (median) frequency of middle ear infections was 2 (1) among infants during the interval period. The maternal education, marital status, and employment status at the time of language assessment of infants is also shown in Table 2. Majority of mothers were married and had completed college and were employed full-time.

Auditory Comprehension Language Score

The mean and SD of the corrected age of the children at the time of language assessment was 38.1 ± 2.1 months. The mean and SD of the chronological age of the children at the time of language assessment was 40.6 ± 2.2 months. The mean and SD of Auditory Comprehension language score was 95 ± 19 (range 50 - 127). Bivariate analyses of Pearson Correlation showed a trend of negative relationship between worse ear IPL and Auditory Comprehension language score ($r = -0.22$, $p = 0.05$) and between better ear IPL and Auditory Comprehension language score ($r = -0.18$, $p = 0.11$). The findings of regression models with the variables included in the final models for the evaluation of the association between I-V IPL (ms) and Auditory Comprehension language score are shown in Table 3. Model 1 evaluates the association between better ear I-V IPL and Auditory Comprehension language score. The better ear I-V IPL was significantly associated with Auditory Comprehension language score after controlling for potential confounders, specifically one unit increase in I-V interpeak latency (or decrease in central nerve conduction velocity) was associated with a decreased score of 5.5 points in Auditory Comprehension language score. In addition, gender, race, ethnicity, and chronic lung disease were also significantly associated with Auditory Comprehension language score after controlling for other clinical factors included in the final model as shown in Table 3. Female gender, Caucasian race, and non-hispanic ethnicity were independently associated with better Auditory Comprehension language score compared to male gender, African-American race, and hispanic ethnicity, respectively. Premature infants with chronic lung disease had lower Auditory Comprehension language score compared to premature infants without chronic lung disease.

Model 2 evaluates the association between worse ear I-V IPL and Auditory Comprehension language score. The worse ear I-V IPL was significantly associated with Auditory

Comprehension language score after controlling for potential confounders, specifically one unit increase in I-V interpeak latency (decrease in central nerve conduction velocity) was associated with a decreased score of 5.4 points in Auditory Comprehension language score. In addition, gender, race, and ethnicity were also significantly associated with Auditory Comprehension language score after controlling for other clinical factors included in the final model as shown in Table 3. Female gender, Caucasian race, and non-hispanic ethnicity were independently associated with better Auditory Comprehension language score compared to male gender, African-American race, and hispanic ethnicity, respectively.

Expressive Communication Language Score

The mean and SD of Expressive Communication language score was 96 ± 16 (range, 52 - 135). The Pearson Correlation analyses showed significant negative correlation between worse ear I-V IPL and Expressive Communication language score ($r = -0.28$, $p = 0.01$) and between better ear I-V IPL and Expressive Communication language score ($r = -0.28$, $p = 0.01$). The findings of regression models with the variables included in the final models for the outcome Expressive Communication language score using each of the primary predictive variables, better ear I-V IPL and worse ear I-V IPL, are shown independently in Table 4.

Model 3 evaluates the association between better ear I-V IPL and Expressive Communication language score. The better ear I-V IPL was significantly associated with Expressive Communication language score after controlling for potential confounders, specifically one unit increase in I-V interpeak latency (decrease in central nerve conduction velocity) was associated with a decreased score of 6.7 points in Expressive Communication language score. In addition, gender, race, and ethnicity were also significantly associated with Expressive Communication language score after controlling for other variables included in the final model as shown in Table 4. Female gender, Caucasian race, and non-hispanic ethnicity were independently associated with better Expressive Communication language score compared to male gender, African-American race, and hispanic ethnicity, respectively.

Model 4 evaluates the association between worse ear I-V IPL and Expressive Communication language score. The worse ear I-V IPL was significantly associated with Expressive Communication language score after controlling for potential confounders, specifically one unit increase in I-V interpeak latency (decrease in central nerve conduction velocity) was associated with a decreased score of 5.6 points in Expressive Communication language score. In addition, gender and ethnicity were also significantly associated with Expressive Communication language score after controlling for other clinical variables included in the final model as shown in Table 4. Female gender and non-hispanic ethnicity were independently associated with better expressive language score compared to male gender and hispanic ethnicity, respectively.

DISCUSSION

During the perinatal period, the human brain development is characterized by an active process of oligodendroglial cell differentiation and maturation which is essential for brain myelination, a neurodevelopmental process that peaks during the period between 2 months

before and after the term age.(2) Infants born prematurely are commonly exposed to perinatal factors such as sepsis and nutritional deficiency that are known to adversely affect oligodendroglial cell differentiation and maturation.(11, 32) Therefore, premature infants are at increased risk for abnormal brain myelination and related abnormal neurodevelopmental outcomes, including language impairment. Recently, ABR has been increasingly used in neonatal clinical studies as a non-invasive objective tool to evaluate the effect of putative perinatal and neonatal factors on perinatal brain development, including myelination.(9-11, 33-37) Although auditory neural myelination evaluated by ABR is increasingly used in neonates as an indirect assessment of brain myelination, its association with later neurodevelopment outcome has not been well studied.(17) Our findings demonstrate that central nerve conduction velocity or I-V IPL, an index of auditory neural myelination, as evaluated by ABR at 35 weeks PMA is associated with subsequent language development at 3 years of age.

Early identification of premature infants at risk for abnormal neurodevelopment is important so that effective intervention can be initiated at an earlier age to reduce neuromorbidity and maximize functional potential. To date, no single clinical or laboratory assessment has been identified to accurately identify premature infants at risk for abnormal long-term neurodevelopmental outcome, specifically language impairment. Neuroimaging with an ultrasound is most commonly used to identify premature infants at risk for abnormal neurodevelopmental outcome. Although abnormal cranial ultrasound findings such as intraventricular hemorrhage and cystic periventricular leukomalacia may be helpful in identifying infants at risk for abnormal neurodevelopmental outcome such as gross motor delay, cranial ultrasound is often normal in premature infants with abnormal neurodevelopmental outcome.(38) More importantly, our findings suggest that neonatal cranial ultrasound findings may not be predictive of language outcome. Although brain MRI may be used to evaluate brain development including myelination, the usefulness of MRI to evaluate brain myelination is limited before term age in premature infants.(4, 6, 7) In addition, MRI is technically difficult to perform and may require sedation. Furthermore, MRI provides structural assessment of myelination, while ABR provides neurophysiological assessment of myelination. Till date, neonatal MRI findings have not been validated as a surrogate outcome for later language outcome in premature infants. Our findings suggest that auditory neural myelination or I-V IPL as evaluated by ABR at 35 weeks PMA may be used as a neonatal predictor of later language development in hospitalized premature infants.

Abnormal brain myelination is one of the primary neuropathological mechanisms underlying abnormal neurodevelopmental outcomes in premature infants.(32) However, we limited the study to the evaluation of language outcome for several reasons. First, language delay is one of the most common developmental problems among premature infants during early childhood. Secondly, it is well established that myelination is critical for efficient and coherent interneuronal communication which is essential for language development.(5) Thirdly, auditory neural myelination which relates to the speed and timing of the conduction of auditory signals from periphery to auditory cortex is essential for normal language development.(3, 17, 39-49) Furthermore, because early intervention may help to improve language outcome and related academic performance at school age, it is critical to identify premature infants at risk for language delay before discharge. Our finding of the association

of central nerve conduction velocity or IPL during the neonatal period with subsequent language outcome at 3 years of age is consistent with previously reported findings in premature infants.(17) Cox et al. prospectively followed 56 very low birth weight infants who had neonatal ABR before discharge and reported that neonatal ABR findings including I-V IPL may predict language, intelligence quotient, and academic achievement at 8 years of age.(17) Similarly, Desai et al. reported significant association between I-V IPL measured during neonatal period and receptive language delay evaluated at 30 months of age in term infants who were treated with extracorporeal membrane oxygenation during the neonatal period.(50)

Although we did not consider evaluation of other neurodevelopmental outcomes, there is ample evidence to suggest that other neurodevelopmental outcomes such as gross motor development may be influenced by the degree of brain myelination.(18, 51, 52) Stockard et al. demonstrated that persistence of prolonged ABR IPL during the neonatal period was predictive of abnormal neurodevelopmental outcome.(18) Similarly, Majnemer et al. in a prospective study demonstrated significant correlation between increased central nerve conduction time or I-V IPL during the neonatal period and gross motor development at one year of age in high-risk premature infants.(51) Majnemer et al. continued to follow the same cohort longitudinally and reported that neonatal ABR finding was associated with intelligence, visual-motor and gross motor function at 5 years of age.(52) The cumulative evidence suggest that neonatal ABR findings, specifically central nerve conduction velocity is predictive of language, cognitive, and motor development during early childhood.

Our finding of the independent association of gender, race, ethnicity, and chronic lung disease with subsequent language outcome at 3 years of age is consistent with previous reports.(27, 28, 31) Premature female infants have been shown to have decreased neonatal morbidity compared to male infants. In addition, premature female infants have also been shown to have maturational advantage, specifically with auditory neural maturation.(53) These may explain our finding of better language outcomes in girls compared to boys. Similarly, our finding of significant association between chronic lung disease with Auditory Comprehension and not with Expressive Communication is consistent with similar previously reported finding in premature infants.(31)

The strengths of our study include its prospective design, high rate of retention of subjects, and the assessment of language outcome by a speech-language pathologist unaware of auditory and clinical findings. In addition, we ruled out middle ear disease and outer hair cell dysfunction which may influence IPL. As part of the study design, we excluded children with head injury requiring rehospitalization, encephalopathy, meningitis, blindness, and delayed conductive or sensori-neural hearing loss to limit the number of confounding factors. Furthermore, we controlled for potential confounders such as socioeconomic status, interval middle ear infections, etc. in regression analyses. The major limitation of our study is that the findings are based on an observational study. However, the association with language outcome was consistent between better ear IPL and worse ear IPL providing internal validity of the study findings. In addition, our findings of the independent association of race, ethnicity, gender, and chronic lung disease with language outcome which are consistent with existing literature provide additional validity to our finding of the

association between auditory neural myelination and language outcome. Although our study was limited to premature infants 33 weeks GA, our findings may be applicable to late preterm and term infants as auditory neural myelination was evaluated at 35 weeks PMA.

In summary, our findings suggest that evaluation of auditory neural myelination at 35 weeks PMA may be useful in identification of premature infants at risk of subsequent language impairment. Besides aiding prognostication, our findings suggest that auditory neural myelination evaluated using ABR during the neonatal period may be used as a surrogate outcome of brain myelination and subsequent language outcome for therapeutic studies of premature infants.

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Abbreviations

MRI	magnetic resonance imaging
GA	gestational age
PMA	post-menstrual age
NICU	Neonatal Intensive Care Unit
ABR	auditory brainstem evoked response
ANM	auditory neural myelination
IPL	interpeak latency
PLS	preschool language scale
TORCH	toxoplasmosis, other infections, rubella, cytomegalovirus infection and herpes simplex
SD	standard deviation

REFERENCES

1. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr.* Dec; 2005 26(6):427–40. PubMed PMID: 16344661. [PubMed: 16344661]
2. Thompson RA, Nelson CA. Developmental science and the media. *Early brain development.* *Am Psychol.* Jan; 2001 56(1):5–15. PubMed PMID: 11242988. [PubMed: 11242988]
3. Aslin RN, Schlaggar BL. Is myelination the precipitating neural event for language development in infants and toddlers? *Neurology.* Feb 14; 2006 66(3):304–5. PubMed PMID: 16476926. [PubMed: 16476926]
4. Woodward LJ, Clark CA, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. *PloS one.* 2012; 7(12):e51879. PubMed PMID: 23284800. Pubmed Central PMCID: 3532310. [PubMed: 23284800]

5. O'Muircheartaigh J, Dean DC 3rd, Dirks H, Waskiewicz N, Lehman K, Jerskey BA, et al. Interactions between white matter asymmetry and language during neurodevelopment. *J Neurosci.* Oct 9; 2013 33(41):16170–7. PubMed PMID: 24107949. Pubmed Central PMCID: 3792458. [PubMed: 24107949]
6. Arzoumanian Y, Mirmiran M, Barnes PD, Woolley K, Ariagno RL, Moseley ME, et al. Diffusion tensor brain imaging findings at term-equivalent age may predict neurologic abnormalities in low birth weight preterm infants. *AJNR Am J Neuroradiol.* Sep; 2003 24(8):1646–53. PubMed PMID: 13679287. [PubMed: 13679287]
7. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med.* Aug 17; 2006 355(7):685–94. PubMed PMID: 16914704. [PubMed: 16914704]
8. Moore JK, Perazzo LM, Braun A. Time course of axonal myelination in the human brainstem auditory pathway. *Hear Res.* Jul; 1995 87(1-2):21–31. PubMed PMID: 8567438. [PubMed: 8567438]
9. Kohelet D, Arbel E, Goldberg M, Arlazzoroff A. Transient neonatal hypothyroxinemia and the auditory brainstem evoked response. *Pediatr Res.* Nov; 1992 32(5):530–1. PubMed PMID: 1480453. [PubMed: 1480453]
10. Tyson JE, Lasky R, Flood D, Mize C, Picone T, Paule CL. Randomized trial of taurine supplementation for infants less than or equal to 1,300-gram birth weight: effect on auditory brainstem-evoked responses. *Pediatrics.* Mar; 1989 83(3):406–15. PubMed PMID: 2645569. [PubMed: 2645569]
11. Amin SB, Orlando M, Wang H. Latent iron deficiency in utero is associated with abnormal auditory neural myelination in ≥ 35 weeks gestational age infants. *J Pediatr.* Nov; 2013 163(5):1267–71. PubMed PMID: 23932211. [PubMed: 23932211]
12. Amin SB, Orlando M. Optimum click rate for neurodevelopmental evaluation using auditory brainstem response in premature infants. *Am J Perinatol.* Sep; 2012 29(8):587–92. PubMed PMID: 22639350. [PubMed: 22639350]
13. Starr A. Auditory brainstem potentials: comments on their use during infant development. *J Clin Neurophysiol.* Jul; 1984 1(3):331–4. PubMed PMID: 6544315. [PubMed: 6544315]
14. Shah SN, Bhargava VK, Johnson RC, McKean CM. Latency changes in brain stem auditory evoked potentials associated with impaired brain myelination. *Exp Neurol.* Jan 1; 1978 58(1):111–8. PubMed PMID: 145371. [PubMed: 145371]
15. Moller AR, Jannetta PJ, Moller MB. Neural generators of brainstem evoked potentials. Results from human intracranial recordings. *Ann Otol Rhinol Laryngol.* Nov-Dec; 1981 90(6 Pt 1):591–6. PubMed PMID: 7316383. [PubMed: 7316383]
16. Fabiani M, Sohmer H, Tait C, Gafni M, Kinarti R. A functional measure of brain activity: brain stem transmission time. *Electroencephalogr Clin Neurophysiol.* Oct; 1979 47(4):483–91. PubMed PMID: 89952. [PubMed: 89952]
17. Cox C, Hack M, Aram D, Borawski E. Neonatal auditory brainstem response failure of very low birth weight infants: 8-year outcome. *Pediatr Res.* Jan; 1992 31(1):68–72. PubMed PMID: 1594334. [PubMed: 1594334]
18. Stockard JE, Stockard JJ, Kleinberg F, Westmoreland BF. Prognostic value of brainstem auditory evoked potentials in neonates. *Arch Neurol.* Jun; 1983 40(6):360–5. PubMed PMID: 6847443. [PubMed: 6847443]
19. Amin SB, Orlando MS, Dalzell LE, Merle KS, Guillet R. Morphological changes in serial auditory brain stem responses in 24 to 32 weeks' gestational age infants during the first week of life. *Ear Hear.* Oct; 1999 20(5):410–8. PubMed PMID: 10526863. [PubMed: 10526863]
20. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr.* Apr; 1978 92(4):529–34. PubMed PMID: 305471. [PubMed: 305471]
21. Foster-Cohen S, Edgin JO, Champion PR, Woodward LJ. Early delayed language development in very preterm infants: evidence from the MacArthur-Bates CDI. *J Child Lang.* Aug; 2007 34(3):655–75. PubMed PMID: 17822143. [PubMed: 17822143]

22. Luu TM, Vohr BR, Schneider KC, Katz KH, Tucker R, Allan WC, et al. Trajectories of receptive language development from 3 to 12 years of age for very preterm children. *Pediatrics*. Jul; 2009 124(1):333–41. PubMed PMID: 19564317. Pubmed Central PMCID: 2704989. [PubMed: 19564317]
23. Winskel H. The effects of an early history of otitis media on children's language and literacy skill development. *Br J Educ Psychol*. Dec; 2006 76(Pt 4):727–44. PubMed PMID: 17094883. [PubMed: 17094883]
24. Rescorla L, Achenbach TM. Use of the language development survey (LDS) in a national probability sample of children 18 to 35 months old. *J Speech Lang Hear Res*. Aug; 2002 45(4): 733–43. PubMed PMID: 12199403. [PubMed: 12199403]
25. Hoff E, Core C, Place S, Rumiche R, Senior M, Parra M. Dual language exposure and early bilingual development. *J Child Lang*. Jan; 2012 39(1):1–27. PubMed PMID: 21418730. [PubMed: 21418730]
26. Barac R, Bialystok E. Bilingual effects on cognitive and linguistic development: role of language, cultural background, and education. *Child Dev*. Mar-Apr; 2012 83(2):413–22. PubMed PMID: 22313034. Pubmed Central PMCID: 3305827. [PubMed: 22313034]
27. Zambrana IM, Ystrom E, Pons F. Impact of gender, maternal education, and birth order on the development of language comprehension: a longitudinal study from 18 to 36 months of age. *J Dev Behav Pediatr*. Feb; 2012 33(2):146–55. PubMed PMID: 22237556. [PubMed: 22237556]
28. Pungello EP, Iruka IU, Dotterer AM, Mills-Koonce R, Reznick JS. The effects of socioeconomic status, race, and parenting on language development in early childhood. *Dev Psychol*. Mar; 2009 45(2):544–57. PubMed PMID: 19271838. [PubMed: 19271838]
29. Cates CB, Dreyer BP, Berkule SB, White LJ, Arevalo JA, Mendelsohn AL. Infant communication and subsequent language development in children from low-income families: the role of early cognitive stimulation. *J Dev Behav Pediatr*. Sep; 2012 33(7):577–85. PubMed PMID: 22947884. Pubmed Central PMCID: 3434454. [PubMed: 22947884]
30. Mendelsohn AL, Mogilner LN, Dreyer BP, Forman JA, Weinstein SC, Broderick M, et al. The impact of a clinic-based literacy intervention on language development in inner-city preschool children. *Pediatrics*. Jan; 2001 107(1):130–4. PubMed PMID: 11134446. [PubMed: 11134446]
31. Lewis BA, Singer LT, Fulton S, Salvator A, Short EJ, Klein N, et al. Speech and language outcomes of children with bronchopulmonary dysplasia. *J Commun Disord*. Sep-Oct; 2002 35(5): 393–406. PubMed PMID: 12194561. [PubMed: 12194561]
32. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed*. Mar; 2008 93(2):F153–61. PubMed PMID: 18296574. [PubMed: 18296574]
33. Amin SB, Merle KS, Orlando MS, Dalzell LE, Guillet R. Brainstem maturation in premature infants as a function of enteral feeding type. *Pediatrics*. Aug; 2000 106(2 Pt 1):318–22. PubMed PMID: 10920158. [PubMed: 10920158]
34. Amin SB, Guillet R. Auditory neural maturation after exposure to multiple courses of antenatal betamethasone in premature infants as evaluated by auditory brainstem response. *Pediatrics*. Mar; 2007 119(3):502–8. PubMed PMID: 17332203. [PubMed: 17332203]
35. Amin SB, Orlando M, Eddins A, MacDonald M, Monczynski C, Wang H. In utero iron status and auditory neural maturation in premature infants as evaluated by auditory brainstem response. *J Pediatr*. Mar; 2009 156(3):377–81. PubMed PMID: 19939407. Pubmed Central PMCID: 2827634. Epub 2009/11/27. eng. [PubMed: 19939407]
36. Jiang ZD, Yin R, Wilkinson AR. Brainstem auditory evoked responses in very low birthweight infants with chronic lung disease. *Eur J Paediatr Neurol*. May; 2007 11(3):153–9. PubMed PMID: 17276109. [PubMed: 17276109]
37. Amin SB, Ahlfors C, Orlando MS, Dalzell LE, Merle KS, Guillet R. Bilirubin and serial auditory brainstem responses in premature infants. *Pediatrics*. Apr; 2001 107(4):664–70. PubMed PMID: 11335741. Epub 2001/05/23. eng. [PubMed: 11335741]
38. Hamrick SE, Miller SP, Leonard C, Glidden DV, Goldstein R, Ramaswamy V, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *J Pediatr*. Nov; 2004 145(5):593–9. PubMed PMID: 15520756. [PubMed: 15520756]

39. Sharma A, Gilley PM, Dorman MF, Baldwin R. Deprivation-induced cortical reorganization in children with cochlear implants. *Int J Audiol.* Sep; 2007 46(9):494–9. PubMed PMID: 17828665. [PubMed: 17828665]
40. Rance G, Barker EJ, Sarant JZ, Ching TY. Receptive language and speech production in children with auditory neuropathy/dyssynchrony type hearing loss. *Ear Hear.* Sep; 2007 28(5):694–702. PubMed PMID: 17804983. [PubMed: 17804983]
41. Rance G, Barker E, Mok M, Dowell R, Rincon A, Garratt R. Speech perception in noise for children with auditory neuropathy/dys-synchrony type hearing loss. *Ear Hear.* Jun; 2007 28(3): 351–60. PubMed PMID: 17485984. [PubMed: 17485984]
42. Neville H, Bavelier D. Human brain plasticity: evidence from sensory deprivation and altered language experience. *Prog Brain Res.* 2002; 138:177–88. PubMed PMID: 12432770. [PubMed: 12432770]
43. Thai-Van H, Cozma S, Boutitie F, Disant F, Truy E, Collet L. The pattern of auditory brainstem response wave V maturation in cochlear-implanted children. *Clin Neurophysiol.* Mar; 2007 118(3):676–89. PubMed PMID: 17223382. [PubMed: 17223382]
44. Sininger YS, Doyle KJ, Moore JK. The case for early identification of hearing loss in children. Auditory system development, experimental auditory deprivation, and development of speech perception and hearing. *Pediatr Clin North Am.* Feb; 1999 46(1):1–14. PubMed PMID: 10079786. [PubMed: 10079786]
45. Mason SM, Mellor DH. Brain-stem, middle latency and late cortical evoked potentials in children with speech and language disorders. *Electroencephalogr Clin Neurophysiol.* Jul; 1984 59(4):297–309. PubMed PMID: 6203719. [PubMed: 6203719]
46. Moore DR. Postnatal development of the mammalian central auditory system and the neural consequences of auditory deprivation. *Acta Otolaryngol Suppl.* 1985; 421:19–30. PubMed PMID: 2994353. [PubMed: 2994353]
47. Kral A, Hartmann R, Tillein J, Heid S, Klinke R. Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. *Cereb Cortex.* Jul; 2000 10(7):714–26. PubMed PMID: 10906318. [PubMed: 10906318]
48. von Suchodoletz W, Wolfram I. Early auditory evoked potentials in children with language development disorders. *Klin Padiatr.* Sep-Oct; 1996 208(5):290–3. PubMed PMID: 8992096. Fruhe akustisch evozierte Potentiale (FAEP) bei Kindern mit Sprachentwicklungsstörungen. [PubMed: 8992096]
49. Fuess VL, Bento RF, da Silveira JA. Delay in maturation of the auditory pathway and its relationship to language acquisition disorders. *Ear Nose Throat J.* Oct; 2002 81(10):706–10. 12. PubMed PMID: 12405091. [PubMed: 12405091]
50. Desai S, Kollros PR, Graziani LJ, Streletz LJ, Goodman M, Stanley C, et al. Sensitivity and specificity of the neonatal brain-stem auditory evoked potential for hearing and language deficits in survivors of extracorporeal membrane oxygenation. *J Pediatr.* Aug; 1997 131(2):233–9. PubMed PMID: 9290609. [PubMed: 9290609]
51. Majnemer A, Rosenblatt B, Riley P. Prognostic significance of the auditory brainstem evoked response in high-risk neonates. *Dev Med Child Neurol.* Feb; 1988 30(1):43–52. PubMed PMID: 3371571. Epub 1988/02/01. eng. [PubMed: 3371571]
52. Majnemer A, Rosenblatt B. Prediction of outcome at school entry in neonatal intensive care unit survivors, with use of clinical and electrophysiologic techniques. *J Pediatr.* Nov; 1995 127(5):823–30. PubMed PMID: 7472846. [PubMed: 7472846]
53. Li M, Zhu L, Mai X, Shao J, Lozoff B, Zhao Z. Sex and gestational age effects on auditory brainstem responses in preterm and term infants. *Early Hum Dev.* Jan; 2013 89(1):43–8. PubMed PMID: 22849808. Pubmed Central PMCID: 3490052. [PubMed: 22849808]

Table 1**Baseline Demographic and Clinical Profile of Study Population**

	(N = 80)
Mean Gestational Age in weeks (*SD, range)	29.2 (2.6, 24.2-32.6)
Mean Birth Weight in grams (SD, range)	1336 (449, 450-2595)
Gender (% Male)	43 (53)
Mode of Delivery (% C-section)	69 (86)
Apgar Score < 3 at 5 minutes (%)	44 (55)
Race (% Caucasians)	1 (1)
Ethnicity (% Non-Hispanic)	49 (61)
Respiratory Distress Syndrome (%)	55 (68)
Grade III/IV Intraventricular Hemorrhage (%)	3 (4)
Cystic Periventricular Leukomalacia (%)	3 (4)
Culture Proven Sepsis (%)	24 (30)
Breast Milk Feeding during NICU stay (%)	64 (80)
Necrotizing Enterocolitis (Pneumatosis or Perforation) (%)	2 (3)
Number of Infants with Chronic Lung Disease (%)	10 (12)

* SD denotes standard deviation

Table 2
Post-discharge Maternal and Child Characteristics

Clinical Characteristics of 80 Subjects	Prevalence
Number of Infants in Early Intervention Program (%)	33 (41)
Number of Infants in Preschool or Day Care (%)	24 (30)
Mean Number of Siblings (Median)	1.4 (1.5)
Number of Bilingual Infants (%)	1 (12)
Number of Infants in Reach Out and Read Program (%)	7 (8.7)
Mean Number of Middle Ear Infections (Median)	2 (1)
Maternal Education	
Number of Mothers with only High School (%)	24 (30)
Number of Mothers with Incomplete College (%)	24 (30)
Number of Mothers with Completed College (%)	32 (40)
Maternal Employment	
Number of Mothers with No Job (%)	30 (38)
Number of Mothers with Part-time Job (%)	13 (16)
Number of Mothers with Full-time Job (%)	37 (46)
Number of Mothers Married (%)	45 (56)

Table 3

Association between Auditory Neural Myelination and Auditory Comprehension Language Score

Model 1: Association between Better Ear I-V Interpeak Latency and Comprehension Language Score	Coefficient	P	95% Confidence Interval
Better Ear I-V Interpeak Latency (ms)	-5.5	0.02	-10.0 – -0.9
Gender (Female vs. Male)	11.5	0.005	4.0 – 19.1
Race (Caucasian vs. African American)	13.9	0.005	6.4 – 21.4
Ethnicity (Hispanic vs. Non Hispanic)	-16.3	0.005	-27.1 – -5.6
Chronic Lung Disease (Yes vs. No)	-11.9	0.03	-23 – -0.88
Feeding (Breast milk vs. Formula)	6.60	0.17	-2.84 – 16.04
Model 2: Association between Worse Ear I-V Interpeak Latency and Comprehension Language Score			
Worse Ear I-V Interpeak Latency (ms)	-5.4	0.02	-9.8 – -0.9
Gender (Female vs. Male)	11.6	0.004	4.0 – 19.1
Race (Caucasian vs. African American)	12.5	0.004	4.9 – 20.2
Ethnicity (Hispanic vs. Non Hispanic)	-16.4	0.01	-27.2 – -5.6
Feeding (Breast milk vs. Formula)	6.98	0.14	-2.44 – 16.39

Table 4

Association between Auditory Neural Myelination and Expressive Communication Language Score

Model 3: Association between Better Ear I-V Interpeak Latency and Expressive Language Score	Coefficient	P	95% Confidence Interval
Better Ear I-V Interpeak Latency (ms)	-6.7	0.001	-10.6 – -2.7
Gender (Female vs. Male)	9.9	0.006	3.5 – 16.4
Race (Caucasian vs. African American)	10.0	0.001	3.5 – 16.5
Ethnicity (Hispanic vs. Non Hispanic)	-16.6	0.002	-25.9 – -7.3
Chronic Lung Disease (Yes vs. No)	-8.8	0.07	-18.2 – 0.6
Middle Ear Infections (Number of Infections)	0.94	0.06	-0.04 – 1.91
Model 4: Association between Worse Ear I-V Interpeak Latency and Expressive Language Score			
Worse ear I-V Interpeak Latency	-5.6	0.003	-9.5 – -1.8
Gender (Female vs. Male)	9.5	0.009	3.0 – 15.9
Race (Caucasian vs. African American)	6.4	0.08	-0.8 – 13.6
Ethnicity (Hispanic vs. Non Hispanic)	-14.7	0.004	-24.3 – -5.1
Chronic Lung Disease (Yes vs. No)	-8.7	0.07	-18.2 – 0.8
Maternal Education	3.27	0.12	-0.92 – 7.45