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Feasibility of event-related potential (ERP) biomarker use to study effects of mother's voice exposure on speech sound differentiation of preterm infants

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ABSTRACT

Atypical maturation of auditory neural processing contributes to preterm-born infants' language delays. Event-related potential (ERP) measurement of speech–sound differentiation might fill a gap in treatment-response biomarkers to auditory interventions. We evaluated whether these markers could measure treatment effects in a quasi-randomized prospective study. Hospitalized preterm infants in passive or active, suck-contingent mother's voice exposure groups were not different at baseline. Post-intervention, the active group had greater increases in/du/-/gu/differentiation in left frontal and temporal regions. Infants with brain injury had lower baseline/ba/-/ga/and/du/-/gu/differentiation than those without. ERP provides valid discriminative, responsive, and predictive biomarkers of infant speech–sound differentiation.

Introduction

Preterm infants are at high risk for early neurosensory impairments and developmental delays that have lasting consequences into school age (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Foster-Cohen, Edgin, Champion, & Woodward, 2007; Maitre, 2015). While the estimated prevalence of language difficulties is 2–19% and specific language impairment 3–7% in the general pediatric population (ASHA, 2015; Conti-Ramsden & Botting, 1999; Siu, 2015), preterm born children are twice as likely to have a severe language delay compared to their term-born peers (Foster-Cohen et al., 2007). By preschool age, very preterm (born <30 weeks gestation) and extremely low birth weight infants (birth weight <1000 g) also have poorer receptive and expressive language development, especially with regards to vocabulary size, quality of word production, syntax, morphology, and comprehension (Howard et al., 2011; Mikkola et al., 2005). These impairments are present in the absence of major disabilities or neurological disorders, independent of socioeconomic status, and can increase in severity from preschool to school age (Hack et al., 1992; Siu, 2015; van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012). Speech and language delays and impairments are prevalent in preterm infants without overt hearing loss (Vohr, 2016). Instead, their delays are more likely related to atypical maturation of auditory neural processing, a developmental process influenced by immaturity at birth, physiological insults, and sound experience.

In particular, speech sound exposure allows the establishment of complex networks necessary for later language production and understanding (Kuhl, 2004). However, the auditory environment of neonatal intensive care units (NICUs) where preterm infants spend the first few months of life is highly atypical (McMahon, Wintermark, & Lahav, 2012). Preterm infants are exposed to unfiltered and loud mechanical noises (Carvalhais, Silva, Xavier, & Santos, 2017). Conversely, they are deprived of infant-directed speech sounds, which may be detrimental to the development of speech processing and language development

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(Caskey, Stephens, Tucker, & Vohr, 2014; Filippa et al., 2017). More infant-directed speech in the NICU is associated with improved neurodevelopmental outcomes in the first 2 years, and early language processing efficiency predicts receptive vocabulary outcomes in 3-year-old children born preterm (Marchman, Adams, Loi, Fernald, & Feldman, 2015). These combined findings have prompted new research in early interventions to improve the language outcomes of preterm infants before they leave the hospital. Many of these interventions target increased amount of exposure to parental speech, especially during periods of optimal infant receptive states (e.g., quiet, alert). Further, research in infant learning provides strong evidence for the importance of reciprocity and contingency in cognitive, emotional, and social development (Bråten, 2009; Esposito, Setoh, Shinohara, & Bornstein, 2017; Gibbon, Berryman, & Thompson, 1974; Kuhl, 2004; Wijnroks, 1997). Learning of language in infants is improved when language exposure is presented contingent on infant action and promptly after the action (Caskey et al., 2014; DeCasper & Carstens, 1981; McMahon et al., 2012; Moon & Fifer, 2000; Naoi et al., 2012). This type of intervention approach may be more beneficial to preterm infants than passive exposure to parent's voice.

However, the design of effective auditory interventions in preterm infants has been limited due to the lack of validated, feasible, and relevant biomarkers to measure treatment response. MRI offers invaluable data about the microstructural organization of the brain, discriminates immaturity from injury, and can be predictive of neurodevelopmental outcomes (Anderson, Cheong, & Thompson, 2015; Novak et al., 2017). However, in NICU infants, its utility as a biomarker is limited by widespread feasibility challenges, need for sleeping patients and lack of rapid response to functional changes. The development of new clinically relevant biomarkers of auditory processing is essential to rational design and effectiveness measurement of language interventions for preterm infants in the NICU.

It was previously determined that infant differentiation of a limited subset of speech sound syllables could be used to objectively quantify the amplitude of auditory processing responses, leveraging event-related potential (ERP) methodology, or time-locked EEG (Key, Lambert, Aschner, & Maitre, 2012). The measures showed an ability to discriminate between levels of immaturity at birth, postnatal age, and most importantly, to predict language outcomes at 1 and 2 years of age. In particular, the/ba/-/ga/ and/du/-/gu/contrasts during the 250–400 ms poststimulus interval in frontal and temporal locations predicted half the variance in cognitive, expressive, and receptive language scores at 2 years on the Bayley Scales of Infant Development III (Maitre, Lambert, Aschner, & Key, 2013). To test whether the previously identified speech sound neurophysiological biomarkers could be responsive to a standardized auditory exposure intervention, we designed a prospective study comparing a cohort of preterm infants in the late preterm period, receiving a mother's voice passively for 2 weeks, to a cohort receiving the same number of treatments in an active, contingent delivery system. We hypothesized that ERP methodology could demonstrate pre- to post-intervention increase in speech sound differentiation as measured by/ba/-/ga/ and/du/-/gu/contrasts during the 250–400 ms poststimulus interval in the frontal and temporal regions, for the infants receiving active parent speech sound exposure intervention. We also hypothesized that this difference may not be present in infants receiving a passive exposure to the same sounds during this short period of time.

Methods

Participants

We conducted a quasi-randomized prospective study in which infants were allocated to either a standardized environmental passive mother's voice exposure protocol (n = 10) and an experimental, active, suck-contingent mother voice exposure condition (n = 10) with infants hospitalized at a NICU. Parents gave consent for study participation according to the Institutional Review Board approved protocol. Participants were eligible if they were between 32 and 34 weeks' postmenstrual age (PMA) at study start, and had a minimum 30 cm head circumference (to fit the smallest available

Table 1. Participant characteristics.

	All $n = 20$	Active exposure $n = 10$	Passive exposure $n = 10$
GA in weeks (median, IQR)	27 (25, 30)	26 (25, 30)	27 (27, 30)
Birth weight in g (median, IQR)	1037 (846,1311)	947 (801,1102)	1236 (884,1543)
PMA at study start (weeks median, IQR)	33 (33, 34)	33 (32, 34)	34 (33, 34)
Sex (% female)	7 (35%)	3 (30%)	4 (40%)
IVH III/IV/PVL (n prior to DC)		4	1
Type of ventilation (n CPAP/NC/RA)	9/7/4	6/3/1	3/4/3
Race (n)			
Caucasian	11	5	6
African-American	8	4	4
Other	1	1	0
Maternal education HS or more (n)	9	4	5
Number of treatment sessions (n median, IQR)	17 (15, 18)	18 (14, 19)	16 (14, 17)
Total treatment session time (minutes median, IQR)	231 (166, 269)	166 (163, 210)	369 (300, 400)

GA: Gestational Age at Birth; Range of GA: 25–31
PMA: Postmenstrual age; Range PMA: 34–37
IVH: Intraventricular hemorrhage
PVL: Periventricular leukomalacia
DC: discharge
CPAP: Continuous Positive Airway Pressure
NC: Nasal Cannula
RA: Room air
HS: High School

ERP net). Of the 20 infants in the study 35% were female, and infants in both groups had similar gestation age at birth (GA) and PMA at study entry (Table 1).

Infants were excluded if they were intubated, or received sedatives or opiates in the 24 hours prior to study start. Infants received clinical cranial ultrasounds during their intensive care stay per standard of care. Infants with all grades of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) on cranial neuroimaging were included in the current study. Infants were assigned utilizing an alternating randomization system to either the standard protocol or the experimental condition. Multiples were randomized into different groups. All infants passed their auditory brain stem response (ABR) hearing screening.

Procedure

A music therapist met with each infant's mother to pre-record her voice singing and reading in an infant-directed manner, alternating song and speech every 5 minutes, for 20 minutes. The sound file was processed to make it seamless and ready to be played for the infant during the intervention sessions (Standley, 2012). The active exposure condition included delivery of the caregivers' audio recording via a Pacifier Activated Lullaby system, an FDA-approved NICU sound player that provides the sound contingent on the infant non-nutritively sucking on a standard pacifier. The passive exposure protocol was an approved clinical protocol that included the same type of caregiver voice audio recording played for the infant through the same device, non-contingently. The passive exposure session was identical to the active one, with the exception of the pacifier-contingent player activation. The session length was selected based on previously published protocols and recommendations for auditory interventions for infants hospitalized in a NICU (Standley, 2012). Active protocol sessions were terminated if the infant did not accept the pacifier spontaneously, if the infant fell asleep, or displayed signs of excessive respiratory effort or autonomic nervous system instability (increased work of breathing as evidenced by intercostal retractions, increased respiratory or heart rate above one standard deviation for PMA, skin color or oxygen saturation changes not resolving spontaneously within 10 seconds, apnea, or bradycardia). All sessions were conducted at

least 3 hours apart. The bedside nursing team decided on the appropriateness of more than one session per day based on the infant's clinical condition. The team made no additional modification of the environment nor gave instructions to the parent. Both types of sessions took place at the infant's bedside, were provided for 10 days during a 2-week period, up to two sessions daily, and lasted a maximum of 20 minutes each (total median exposure 166 minutes, IQR 163–210) for active (total median exposure 369 minutes, IQR 300–400) and for passive (Table 1).

ERP recording and analysis

The sound levels of the session stimuli were kept to the recommended standard for the NICU, under an hourly average of 55 dBA (White, 2007). The ERP assessment or interventions administering therapists insured an auditory appropriate environment prior to data collections. Noise level was checked prior to the session, the session started only when the environmental noise was confirmed to be at or under the recommended limit. Concerns about infants not hearing mother's voice above the background of airflow were alleviated by observing clear contingent behavioral responses (suck) upon auditory stimulation.

A high-density array of 128 electrodes embedded in soft sponges (Hydrocel Sensor Net, EGI, Inc., Eugene, OR) were used to record ERPs with a sampling rate of 1000 Hz, filters set to 0.1–400 Hz. Recording of brainwaves were controlled by Net Station (v. 4.3; EGI, Inc., Eugene, OR). E-Prime (v. 2.0, PST, Inc., Pittsburgh, PA) software control stimulus delivery, the stimulus was delivered through a portable speaker (JVL by HARMAN, Inc., Stamford, CT) with a frequency response of 120 Hz–20 kHz (−6 dB), placed 6 inches above the infant's head and connected with single 3.5 mm auxiliary cord. The stimuli were presented at 60 dBA. The ERP speech sound paradigm included a computer-generated woman's voicing one of six syllables (/ba/,/da/,/ga/,/bu/,/du/,/gu/) randomly and at random intertrial intervals for a total of 25 trials per syllables over 7–10 minutes. Intertrial intervals varied between 1600 ms and 2600 ms. More than the four key stimuli (/ba/,/ga/,/du/,/gu/) were presented to prevent habituation (Key et al., 2012). The experiment was programmed to present all six sounds once, before the sequence was re-randomized. Thus, the same sound could be presented no more than two times in a row.

The stimulus presentation paradigm allowed collection of the data and the replication of prior-identified time windows and scalp regions quantifying individual differences in speech sound processing. Recordings were filtered and segmented. Each trial included a 200 ms pre-stimulus baseline and a 800 ms poststimulus interval. Individual ERP recordings' baseline were corrected and referenced to an average reference through an automated script and bad channels were reconstructed using spherical spline interpolation procedures built-in to NetStation software (any channel with voltage exceeding 200 μV was considered bad). Trials with ocular or sucking artifacts were excluded through the Netstation automated algorithm. A team member masked to group allocation performed an additional off-line channel processing. If more than 15 electrodes' recordings within a single trial were considered poor through this additional review, the entire trial was discarded. For a data set to be included in the statistical analyses, each stimulus condition had to have a minimum of 10 retained trials. Trial retention rates were comparable across conditions and with published literature in infants. Final averages were based on a mean of 15.55 (SD = 4.89) trials per condition. After artifact detection, individual ERPs were averaged and baseline corrected by subtracting the average microvolt value across the 200-ms pre-stimulus interval from the poststimulus segment. Mean amplitudes were calculated for each selected electrode location (F3: frontal left, F4: frontal right, T5: temporal left, T6: temporal right—identified in prior published studies (Maitre et al., 2014, 2013) by averaging ERP readings for each speech sound in the 250–400 ms interval after stimulus onset. This specified time window was based on previous publications reporting work with pediatric populations and consistent with the aim of evaluating auditory speech sound differentiation in preterm infants (Friedrich, Weber, & Friederici, 2004; Kushnerenko et al., 2002). Grand averaged responses at all selected scalp locations are shown in Figure 1.

The absolute difference in mean amplitude was calculated for each speech sound. This value corresponded to the strength of the differentiation between/ba/and/ga/ and between/du/and/gu/

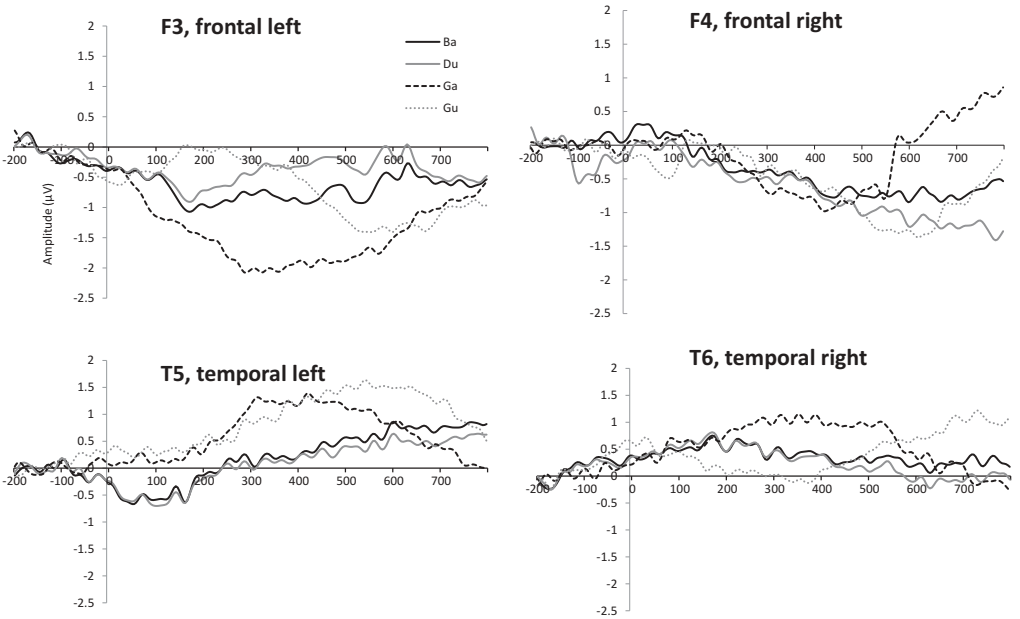

Figure 1. Grand average tracings of event-related potentials (ERP) responses to individual speech-sounds at baseline. Each tracing represents averaged ERP tracings for each sound at the pre-specified locations. Auditory stimuli are presented at time 0ms. Box represents time window for calculation of mean amplitude of response. Tracings are averaged over all 20 infants in the study prior to the intervention. F3, frontal left; F4, frontal right; T5, temporal left; T6, temporal right.

sounds, in microvolts. Visualization of absolute difference for the two sound contrasts in left frontal location can be seen in Figure 2.

Pre-intervention responses were compared between treatment groups and separately, and between groups with and without white matter injury (WMI) using a correlational analysis controlling for GA and PMA. Associations between GA and ERP responses were examined using linear regressions. Associations between ERP responses, GA, and WMI were examined using multivariable modeling. Changes between pre and post each intervention were analyzed at the individual level using paired two-tailed, t-tests. Traditional statistical criteria ($p < 0.05$, two-tailed) were used.

All statistical analyses were completed on software SPSS version 20 (IBM SPSS Statistics, Chicago, IL, USA) and SAS version 9.2 (Proc MIXED; SAS Inc., Cary, NC, USA).

Results

In this proof of concept study, both interventions were feasibly administered while infants were receiving continuous positive airway pressure (CPAP), nasal cannula (NC), and room air (RA). The study population included infants on all three types of respiratory support typical of preterm infants cared for at late PMA. Pre-intervention ERP responses were similar in both groups (Table 2).

First, we ensured that our biomarkers of speech sound differentiation were consistently associated with the previous findings showing a positive association with increasing GA at birth. Across frontal right and temporal left scalp locations, baseline differentiation of the/ba//ga/contrast increased with increasing GA ($r = .511$, $p = 0.02$, and $r = 656$, $p = 0.002$, respectively). When considering all scalp locations in all patients, GA explained 42.1% of the variance in the amplitude of/ba//ga/differentiation ($p = 0.002$). The/du//gu/contrast showed a similar but nonsignificant trend (9.8% $p = 0.178$). Since one-fourth of our population had severe WMI on ultrasound, we examined differences in speech sound contrasts at

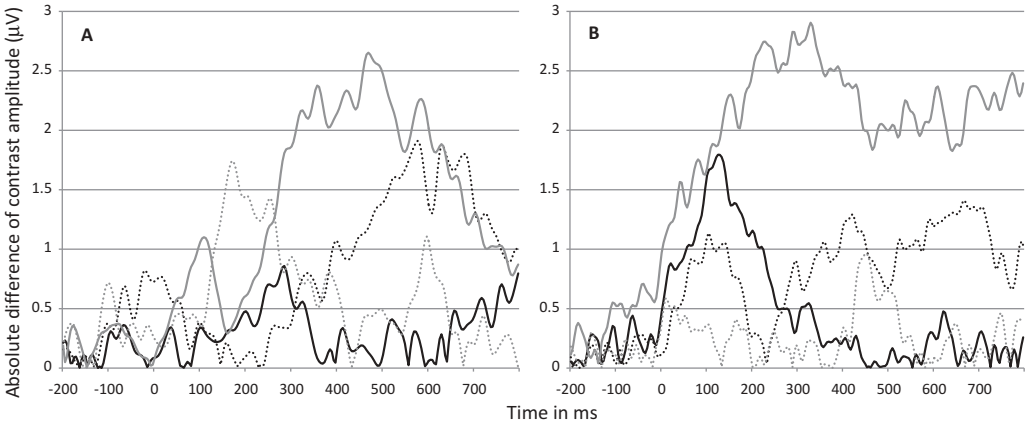

Figure 2. Characteristics of event-related potentials (ERP) measuring speech-sound differentiation in left frontal location at baseline (A) and post intervention (B). Each tracing represents the absolute difference of averaged ERP tracings for each sound contrast at the pre-specified locations. Auditory stimuli are presented at time 0 ms. Tracings are averaged for infants in each group. Tracing correspond to the following: Black line solid: active group du-gu; black line dotted: active group ba-ga Grey line solid: passive group du-gu; grey line dotted: passive group ba-ga.

Table 2. Baseline ERP amplitude responses in μV *.

Location	Sound contrast	All (n = 20)	Active exposure (n = 10)	Passive exposure (n = 10)	p
F3	/ba//ga/	2.01 (1.39)	2.31 (1.4)	1.71 (1.3)	0.36
	/du//gu/	2.35 (2.14)	1.92 (1.2)	2.77 (2.7)	0.40
F4	/ba//ga/	2.7 (2.17)	2.20 (1.3)	3.20 (2.7)	0.33
	/du//gu/	3.64 (3.75)	3.77 (2.8)	3.50 (4.5)	0.88
T5	/ba//ga/	3.68 (3.73)	3.01 (2.2)	4.35 (4.7)	0.45
	/du//gu/	3.27 (2.57)	3.61 (2.9)	2.92 (2.1)	0.57
T6	/ba//ga/	2.77 (2.13)	3.38 (1.8)	2.15 (2.2)	0.22
	/du//gu/	2.34 (1.79)	2.24 (1.8)	2.44 (1.7)	0.83

*all responses indicated as mean (SD) in microvolts
ERP: event-related potential
F3: frontal left
F4: frontal right
T5: temporal left
T6: temporal right
p is two-tailed, adjusted for gestational age at birth and age at event-related potential assessment

baseline between groups with and without WMI using a group-level, one-way ANOVA. Mean differentiation amplitude of/ba//ga/(absolute difference of mean amplitude for each speech sound in the 250–400 ms window) was significantly higher in the no WMI compared to the WMI group at frontal right (3.19 vs. 1.23 μV; p = 0.04), temporal left (4.49 vs. 1.24 μV p = 0.05) and of/du//gu/at temporal left (3.92 vs.1.3 μV p = 0.03). No significant effects were found at frontal left and frontal right locations. However, because lower GAs are associated with an increased likelihood of WMI, a more accurate representation was obtained from a multivariable model, incorporating both presence of WMI and GA as predictors of/ba//ga/differentiation amplitude. Overall, this model explained 43.6% of the variance in temporal left location/ba//ga/(p = 0.008) with standardized β coefficients of −0.105 for presence of WMI and 0.726 for GA (Table 3).

Next, we examined whether our biomarkers could detect a response to active compared to the passive language exposure. Table 4 demonstrates baseline versus postexposure mean amplitudes of the/du//gu/and/ba//ga/contrasts. While the groups were not different for any variable at baseline, after the intervention the contingent language group had significantly higher/du//gu/differentiation amplitude than the passive language exposure group in frontal left and temporal right (*all p < 0.05*,

Table 3. White matter injury and ERP responses comparison.

		No WMI $n = 15$	WMI $n = 5$	p
F3	/ba//ga/	2.21 (1.48)	1.41 (0.86)	0.14
	/du//gu/	2.5 (2.34)	1.9 (1.29)	0.30
F4	/ba//ga/	3.19 (2.27)	1.23 (0.69)	**0.04***
	/du//gu/	4.33 (4.04)	1.55 (1.25)	0.08
T5	/ba//ga/	4.49 (3.97)	1.24 (0.65)	**0.05***
	/du//gu/	3.92 (2.59)	1.3 (1.11)	**0.03***
T6	/ba//ga/	2.97 (2.23)	2.15 (1.63)	0.24
	/du//gu/	2.76 (1.84)	1.09 (0.80)	0.04

*all responses indicated as mean (SD) in microvolts
ERP: event-related potential
WMI: white matter injury
F3: frontal left
F4: frontal right
T5: temporal left
T6: temporal right
p is significance for two-tailed t-test

Table 4. Difference in pre-post differentiation amplitude in μV.

		Passive exposure $n = 10$	Active exposure $n = 10$
F3	/ba//ga/	0.42	1.04
	/du//gu/	−1.10	2.87*
F4	/ba//ga/	−1.37	0.15
	/du//gu/	−1.14	−0.81
T5	/ba//ga/	−2.34	−0.03
	/du//gu/	−0.61	0.068
T6	/ba//ga/	0.11	0.20
	/du//gu/	−0.27	2.53*

* significance<0.05 for two-tailed t-test compared to baseline for condition
F3: frontal left
F4: frontal right
T5: temporal left
T6: temporal right

USA. Because of the importance of GA at birth and of WMI presence, we examined models predicting improvements in/du//gu/differentiation in frontal left and temporal right locations between pre- and posttreatment. Addition of WMI and GA did not improve precision of the model in either frontal left or temporal right locations. Therefore, we calculated the effect size on/du//gu/differentiation for active versus passive exposure as a Cohen's $d = 1.15$ ($p = 0.01$) at frontal left and Cohen's $d = 0.83$ ($p = 0.04$) at temporal right locations.

Discussion

The current study demonstrates for the first time the feasibility of using amplitude of cortical responses to prespecified speech sounds in preterm infants, to measure the effects of meaningful speech exposure in the NICU. We confirmed that as in previous studies, speech sound differentiation is a sensitive biomarker of the degree of immaturity of preterm infants. We also showed that speech sound differentiation was lower at equivalent PMA in infants who had severe neural insults on the spectrum of encephalopathy of prematurity. We then measured change from baseline after contingent exposure in contrast to passive exposure. Our biomarkers showed that the two exposure groups did not have measurable differences at baseline, but did so after the 2-week interventions. In this pilot study differentiation of/du//gu/and/ba//ga/contrasts was sensitive to the degree of immaturity at birth, as

in larger studies (Key et al., 2012; Maitre et al., 2013). PMA was extremely homogeneous due to the inclusion criteria for the study, making an investigation of postnatal age unfeasible.

Early language development is dependent on maturation of the auditory system, and early discriminatory sound abilities are specifically based on the phonetic properties of sounds (Benasich, Choudhury, Realpe-Bonilla, & Roesler, 2014). During the first months of development, initially broad discrimination abilities narrow as infants begin to learn their native language. Similarly, the discrimination of speech sounds in infants is driven by acoustic properties of stimuli, with exposure and experience guiding the development of increasing sensitivity to relevant sound features (Scott, Pascalis, & Nelson, 2007). The speech sounds used in the current study represent distinct phonetic categories and thus should be differentiated even by a relatively immature auditory system.

Previously, we showed that this ability to differentiate between specific early speech sounds is directly associated with maturity at birth and later neurodevelopmental outcomes. Both GA at birth and PMA influenced the differentiation of consonant contrasts in a cohort of NICU infants. Increasing PMA for infants born at or after 30 weeks' gestation was associated with increased differentiation (Key et al., 2012). Supporting evidence can also be found in a publication by Guttorm and colleagues (Guttorm, Leppänen, Richardson, & Lyytinen, 2001). Here, the authors found that infants at risk for dyslexia had larger, more positive cortical responses on ERP to the/ga/sound than to/ba/and/da/sounds in the right hemisphere. Typically developing children had responses to/ba/and/da/that differed between anterior and posterior electrode locations.

In addition, our exploratory analysis showed that speech sound differentiation might also be sensitive to the presence of WMI. This was not previously observed, as the normative samples in published studies excluded infants with WMI (Key et al., 2012; Maitre et al., 2017). The finding that preterm infants with WMI had lower speech sound differentiation than their peers without overt neural insults is consistent with a well-established body of literature on the neurodevelopmental delays or disabilities in infants with white matter insults (Elitt & Rosenberg, 2014; Guo et al., 2017; Rollins et al., 2017; Volpe, 2015). In addition, a novel EEG study demonstrated that connectivity of resting state networks was significantly reduced in preterm infants with brain insults compared to those without. Connectivity was altered globally, without spatial correlations to lesion site and more importantly, was associated with Griffiths' developmental quotients at 2 years (Omidvarnia, Metsäranta, Lano, & Vanhatalo, 2015). It is possible to speculate that neural processing of stimuli may be adversely affected by reduced connectivity in our study's preterm infants with severe WMI.

Of the two sound combinations, /du//gu/and/ba//ga/contrasts both appeared to correlate with prematurity at birth and WMI, but only/du//gu/appeared responsive to active treatment. Improvements in/du//gu/differentiation are predictive in previous studies of improved receptive language scores at 2 years of age (Maitre et al., 2013). The effect size of the active versus passive exposure on/du//gu/differentiation appeared large to very large based on *Cohen's d*. However, this pilot study has a small sample size and our findings may not indicate particular enhancement of one sound contrast over another or a large effect of the treatment. No other effect sizes were calculated, as with so few participants any effects would be inflated and purely conjectural.

New knowledge in infants is derived by inferring connections between comparatively small inputs of sensory data (Gopnik & Schulz, 2004; Gweon, Tenenbaum, & Schulz, 2010). This is especially true if exposures are presented contingent on infant action and promptly after the action. For language, this precept holds true even in early pre-linguistic phases, when infants are learning to differentiate among speech sounds. While our study is a quasi-randomized pilot, and we cannot infer causation from our results, these precepts may hold true in preterm infants as well. Preterm infants' cortical speech sound differentiation potentially improves after a 2-week intervention of exposure to mother's voice contingent on sucking, compared to no measurable improvement over this same short period with a noncontingent passive exposure.

Previous animal (Engineer, Centanni, Im, & Kilgard, 2014; Engineer et al., 2015) and human (Santos, Joly-Pottuz, Moreno, Habib, & Besson, 2007) studies have reported that ERP methodologies could offer quantitative and sensitive measurements of cortical processing changes after an intervention, for example

in the case of children with autism spectrum disorders and dyslexia (Carter et al., 2011; Dawson et al., 2010; Santos et al., 2007). In animal models utilizing contingent learning, an intensive 3-week discriminatory expressive speech sound training with rodents (exposed to antiepileptic drug valproic acid to simulate symptoms of autism) resulted in increased amplitude and latency of anterior auditory field responses compared to untrained and typically developing rodents. The neural response was then consistently generalized to successful processing of other sounds that were not a part of the training (Engineer et al., 2014). Pediatric studies in older children with autism spectrum disorders and dyslexia or otherwise impaired reading skills report that baseline cortical speech sound processing differs in strength and latency of the response compared to those of typically developing peers (Friedman & Choudhury, 2005; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Lovio, Halttunen, Lyytinen, Näätänen, & Kujala, 2012; Roberts et al., 2010; Santos et al., 2007; Whitehouse & Bishop, 2008; Yoder, Molfese, Murray, & Key, 2013). ERPs speech sound processing paradigms were used to demonstrate the change of signal processing with children after training interventions such as intensive comprehensive early intervention services, language-specific phonic and grammar training, or speech sound training. ERP methodology showed increased speed and strength of responses after training (Dawson et al., 2012; Russo, Hornickel, Nicol, Zecker, & Kraus, 2010). However, no studies to date have reported ERP measured changes in cortical speech sound differentiation after active auditory training with neonates.

The sound environment of the NICU for preterm infants is noisy and unnatural, leading to concerns for how it may alter the development of speech sound processing in the immature brain. The importance of the auditory environment was demonstrated using ERP measurement of speech sound contrasts in rodents with Rett syndrome: while they had typical speech sound processing measures in a quiet environment, 3 weeks of training improved their abilities in a noisy environment (Engineer et al., 2015). The sound environment during ERP testing is therefore important to consider in studies of preterm infants (Engineer et al., 2015). Of the participants in our study, 45% were on CPAP, an air pressure support system that in combination with environmental noise can vary between 46 and 75 dB (A) at infant's ear (Hamm, Chorna, Thomas, Sowers, & Maitre, 2017). It is encouraging to consider, based on our results and previous studies (Friedman & Choudhury, 2005; Lovio et al., 2012; Santos et al., 2007; Yoder et al., 2013), that speech sound training interventions and ERP's capacity to measure speech sound differentiation seem to overcome the noise barrier, even generated by CPAP.

Lastly, left lateralization of cortical response to speech sounds as measured by ERP have been reported in the past, including in preterm-born infants. Lateralization of both phonetic and tone/pitch differentiation is consistent with the more general lateralization of processing of all sensory stimuli (Hickok & Poeppel, 2007; Zatorre, Evans, Meyer, & Gjedde, 1992). A dual-stream speech sounds processing model also supports lateralization of speech processing with the left hemisphere frontal focus of the dorsal stream being associated with acoustic signals processing (Hickok & Poeppel, 2007). In general, regardless of the hypothesis used to explain how lateralization of speech sound processing to the left occurs throughout development, lateralization is an essential developmental step in the acquisition of necessary brain subsystems and specialization for language (Minagawa-Kawai, 2011). The finding that this process may start in preterm infants is consistent with prior work on the topic.

In the current study, the finding that contingent exposure to speech sounds may increase lateralization more than passive exposure is also consistent with models of development in which combined signal-driven maturation and learning allow progressive establishment of more complex language networks (Minagawa-Kawai, 2011). It is possible that active exposure contributes to learning above signal exposure and enhances the recognition of phonological features such as those used in our ERP paradigm, with increased amplitude of differentiation and lateralization. Maitre and colleagues (2013) reported that difference in the ability to differentiate/ba/and/ga/in the left temporal location predicted a 1-point increase in receptive language score on the standard developmental assessment (Bayley Scales of Infant and Toddler Development III). This, along with the current findings suggest that in infants born preterm, the near-term period represents an intermediate and potentially modifiable step in the continuum of increasing specialization and left-side dominance necessary for higher processes in language acquisition.

Although the current study was a quasi-randomized controlled trial, we did not attempt to infer causality of the results, given the less rigorous nature of randomization than would have been desirable in a clinical trial. The limitations of this study include its small sample size, and the utilization of a computer generated rather than individual maternal voice audio files for measurement of speech sound contrasts. Given the small number of infants included into our study, replication with a larger sample is desirable. In addition, the study was not sufficiently powered to assess other clinical variables, including single or open room environment, or amount of caregivers' presence and other infant-directed speech at bedside.

In conclusion, contingent on further large prospective studies, amplitude of cortical responses to speech sound contrasts using ERP methodology in the NICU could be a valid discriminative, responsive, and predictive biomarker of infant speech sound differentiation.

Declaration of interest

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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