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The cerebral hemodynamic response to phonetic changes of speech in preterm and term infants: The impact of postmenstrual age

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ABSTRACT

Higher brain dysfunction, such as language delay, is a major concern among preterm infants. Cerebral substrates of cognitive development in preterm infants remain elusive, partly because of limited methods. The present study focuses on hemodynamic response patterns for brain function by using near-infrared spectroscopy. Specifically, the study investigates gestational differences in the hemodynamic response pattern evoked in response to phonetic changes of speech and cerebral hemispheric specialization of the auditory area in preterm infants (n = 60) and term infants (n = 20). Eighty neonates born between 26 and 41 weeks of gestational age (GA) were tested from 33 to 41 weeks of postmenstrual age (PMA). We analyzed the hemodynamic response pattern to phonemic and prosodic contrasts for multiple channels on temporal regions and the laterality index of the auditory area. Preterm infants younger than 39 weeks of PMA showed significantly atypical hemodynamic patterns, with an inverted response shape. Partial correlation analysis of the typicality score of hemodynamic response revealed a significant positive correlation with PMA. The laterality index of preterm infants from 39 weeks of PMA demonstrated a tendency rightward dominance for prosodic changes similar to term infants. We provide new evidence that alterations in hemodynamic regulation and the functional system for phonemic and prosodic processing in preterm infants catch up by their projected due dates.

1. Introduction

Major disabilities in preterm infants are becoming less frequent as medical technologies advance. However, higher rates of brain dysfunction in such infants compared with term infants remain an issue (Mwaniki et al., 2012). Even if preterm infants do not present with major central nervous system disorders or other significant complications (e.g., grade 2 to 4 intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, BPD or necrotizing enterocolitis, NEC) at discharge from hospital, higher brain dysfunctions may appear during development (Luu et al., 2009; Aarnoudse-Moens et al., 2009). Such dysfunctions in the cognitive system can be examined by neuroimaging of the brain function and brain anatomy of infants. However, assessment of the hemodynamic response function to cognitive processing could also reveal some aspects of physiological traits of higher brain functions.

Higher brain dysfunction should be identified in the early stages of development to enable early intervention. However, methods for early detection among preterm infants have not yet been established (Mento and Bisiacchi, 2012). Development of such methods is hindered by the lack of research into the neuronal substrates associated with early speech perception in preterm infants, even though this is one of the most important higher brain functions (Mento and Bisiacchi, 2012; Tusor et al., 2014). Studying these processes in preterm infants will provide insights into early developmental milestones and the relationship between brain maturity and function.

EEG studies of term and preterm infants have provided evidence of the neuronal processes underlying early speech perception, with a particular focus on auditory-evoked potentials called mismatch negativity (MMN). For instance, prematurely born infants exhibited MMN to phonemic contrasts of /y/ and /i/, suggesting they had the ability to discriminate between them (Cheour-Luhtanen et al., 1996). However,

Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; MMN, mismatch negativity; PMA, postmenstrual age; fNIRS, functional near-infrared spectroscopy; Oxy, oxygenated; Deoxy, deoxygenated; HRF, hemodynamic response function; GA, gestational age; PNA, postnatal age; SOA, stimulus onset asynchrony; ROI, region of interest; BOLD, blood oxygenation level dependent; IQR, interquartile range

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preterm infants tend to show smaller MMN amplitude than do age-matched full-term infants in their first year of life (Alho et al., 1990). Likewise, recent EEG studies have reported that neural maturation, reflected by postmenstrual age (PMA), has a large impact on speech discrimination (Pena et al., 2010; Bisiacchi et al., 2009). EEG studies have also revealed the developmental course of language-specific phonemic processing, showing developmental changes to produce stronger MMN to native phonemic contrast (Cheour et al., 1998; Dehaene-Lambertz and Gliga, 2004). Moreover, the MMN index in 7.5-month-olds was shown to predict language development at 2 years old (Kuhl et al., 2008).

Although EEG studies have provided accumulating evidence on the functional neurodevelopment as reviewed above, functional near-infrared spectroscopy (fNIRS) is an emerging neuroimaging technique that can strengthen the role of EEG study in the understanding of brain development. This technique has better spatial resolution and so can increase our knowledge of the cerebral substrates for receptive language in preterm infants, particularly hemispheric specialization of specific brain regions. Although the temporal resolution of fNIRS is lower than that of EEG, fNIRS uses an infant-friendly headset without any paste or gel and is a more portable system, which has better temporal resolution (10 Hz) than fMRI. fNIRS measures neuronal activity reflected in changes in concentrations of oxygenated (oxy-) Hb and deoxygenated (deoxy-) Hb and it has been used to identify various neurocognitive developmental processes in infants (Minagawa-Kawai et al., 2011; Gervain et al., 2011; Minagawa-Kawai et al., 2008). Such findings have elucidated the cerebral responses of infants to two spoken language components: phonemes and prosody (Sato et al., 2003; Arimitsu et al., 2011). Phonemic structures (e.g., vowels and consonants) tend to be processed predominantly in the left temporal area, while prosody (e.g., intonations or rhythms) activates the right side more in both children and adults. This functional hemispheric specialization is called functional cerebral laterality of the auditory cortices and it facilitates efficient processing in the cerebral cortex (Minagawa-Kawai et al., 2011; Sato et al., 2003; Arimitsu et al., 2011).

Although language comprehension involves various processes, the perceptual analysis of phonemes and prosody is a crucial initial step for language acquisition in the first year of life. Indeed, perceptual analysis of phonemes deeply affects an infant's learning of their native language. Likewise, prosody is important, because it provides various cues, such as pitch changes, intensity, and rhythmic structures—all of which facilitate the infant's speech acquisition, as exemplified by infant-directed speech offering rich prosodic cues.

Apart from the investigations of cognitive functions stated above, fNIRS is also one of the significant tools to examine hemodynamic physiology in infants as well as in adults. Typical hemodynamic activity of the adult cerebral cortex is characterized by an increase in oxy-Hb and a slight decrease in deoxy-Hb. This is known as the hemodynamic response function (HRF) (Boynton et al., 1996; Friston et al., 2000). However, the development of the HRF pattern in the human brain remained unclear, and some fNIRS studies reported an inverted HRF pattern for young infants in response to perceptual stimuli, whereas some studies did not (Minagawa-Kawai et al., 2008; Sato et al., 2003; Arimitsu et al., 2011). This has been a controversial issue, and evidence of its presence in preterm infants is particularly sparse, partly because the fNIRS investigation of HRF is a relatively new subject. Notably, a recent fNIRS study reported developmental changes in phase differences of oxy- and deoxy-Hb in preterm infants (Watanabe et al., 2017). Although such developmental changes in neurovascular regulation are very intriguing, these results come only from resting-state measurements; HRF patterns during perceptual or cognitive processing should also be investigated.

Consequently, the present study attempts to determine developmental differences in the HRF in response to different functional speech stimuli in preterm and term infants at each PMA. For stimuli, we employed well-established instances of linguistic contrast (phonemic and prosodic contrasts) that are crucial for early language development, as mentioned above. In this study, we specifically examined two aspects of the brain response in neonates: (a) the hemodynamic response pattern of oxygenated (oxy)-Hb changes and (b) functional hemispheric specialization in the temporal cortices. We chiefly focused on PMA, also taking gestational age (GA), post-natal age (PNA), and birth weight into consideration, because HRF is closely related to the physiological development of neonates' vascular systems, which may continuously develop before and after birth. Furthermore, as stated above, the EEG literature on speech perception has reported a significant role of neural maturation corresponding to PMA.

Previous fNIRS studies have also reported increased functional hemispheric specialization during development in the first year of life, reporting developmental changes in laterality but with a normal HRF in every age group. However, no study so far has attempted to examine functional cerebral laterality and HRF regulations in preterm infants (Minagawa-Kawai et al., 2011). We therefore explore whether preterm infants show functional cerebral laterality similar to that reported in term infants.

2. Methods

2.1. Participants

The parents of participants were approached for consent and enrollment between 2010 and 2012. The study included 20 term and 60 preterm neonates, who were all from monolingual Japanese families. Participants were divided into four groups according to their PMA at time of examination. Demographic data for each group are shown in Table 1. An additional 16 neonates were excluded because of noise due to motion artifacts and/or loose probe attachments.

The GA was determined by an obstetrician using data including the last menstrual period, the first accurate ultrasound examination, and assistive reproductive technology. We excluded infants with chromosomal or congenital anomalies including congenital heart anomalies, grade 2 to 4 intraventricular hemorrhage, periventricular leukomalacia, moderate and severe BPD defined as per the National Institutes of Health criteria, NEC, deafness diagnosed by automated auditory brainstem response and those who were medically unstable (Jobe and Bancalari, 2001). Ductus arteriosus was clinically closed at the time of

Table 1
Characteristics of participating infants grouped by PMA at time of examination. IQR stands for interquartile range.

	Preterm infants			Term infants
Group of CGA at the examination	33–35 weeks (n = 27)	36–38 weeks (n = 17)	39–41 weeks (n = 16)	37–41 weeks (n = 20)
Male, n (%)	14 (51.9)	8 (47.1)	7 (43.8)	9 (45.0)
Age at the examination, days, median (IQR)	16 (12–27.5)	17 (9–29)	49 (43.75–56)	4 (3.75–6.25)
GA at birth, weeks, median (IQR)	32 (30 – 33)	33 (32–35)	32 (31–34)	38 (37–39)
Birth weight, g, median (IQR)	1668 (1313–1898)	1733 (1421–1834)	1614 (1453–1846)	2798 (2705–3029)
Apgar score at 1 min, median (IQR)	7 (5.5–8)	8 (6–8)	7 (4.75–8)	8 (8–9)
Apgar score at 5 min, median (IQR)	8 (7.5–9)	9 (8–9)	8 (8–9)	9 (9–9)
Weight at the examination, g, median (IQR)	1886 (1773–2046)	1940 (1850–2228)	3007 (2980–3302)	2735 (2638–2948)