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14 Preliminary Report on Differences in Cerebral Hemodynamic Responses to Mother's Voice between Preterm and Term Neonates

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I. Introduction

Many premature neonates are hospitalized in neonatal intensive care unit (NICU), and this can decrease their chances of hearing *motherese* (infant-directed speech). This may have some effect on their brain development. Therefore, it is important to develop methods of measuring the extent of information that a neonate can get by hearing its mother's voice and the level of familiarity neonates have with their mother's voice. However, it is not yet understood how to identify the level of familiarity of a voice from brain function imaging data. In previous studies, the cerebral hemodynamic response curves to the sound of a human voice indicated a single-peak type response (Nishida, *et al*., 2009; Telkemeyer, *et al*., 2009; Minagawa-Kawai, *et al*., 2011; Sato, *et al*., 2011; Arimitsu, *et al*., 2011). However, the more

familiar neonates are with the voice sound stimulus, the greater is the variety of brain functions that could be executed continuously at different timings, thus showing a multiple-peak response type for some cortical regions. For this response type, a new method alternative to the averaging approach method that has been applied to the single-peak type responses in the previous studies is needed. The purpose of this study was to extract a neonate's specific response to its mother's voice, even from the complex multiple-peak response type curve. In this study, we focused on the peak latency of the hemodynamic response curves and tried to evaluate the complex brain activities that occur during the hearing of a mother's voice for two groups of neonates–term and preterm.

II. Methods

1. Participants

Participants in this study included fifteen term neonates (mean gestational age: 39.3 weeks [range: 38–41], mean postconceptional age: 40.2 [range: 39–41] weeks, 2–7 days old after birth–11 girls and 4 boys) and fourteen preterm neonates (mean gestational age: 31.9 [range: 24–34] weeks, mean postconceptional age: 35.4 [range: 35–43] weeks, 9–56 days old after birth-7 girls and 7 boys). The mean birth weight was 3088 g (range: 2690–3676 g) for term neonates and 1529 g (range: 986–1980 g) for preterm neonates. The neonates' auditory ability was also assessed as normal by means of an automated auditory brainstem response. Written informed consent was obtained from parents before the neonates' participation. This study was approved by the ethical committee of Keio University Hospital (No.2009–189).

2. Stimuli and Procedure

There were 2 conditions for the auditory stimuli–the mother's voice and a female stranger's voice; both were recorded using a digital voice recorder. All speech stimuli comprised a series of short sentences with the rich intonation characteristic of motherese in a Japanese original script. The length of each stimulus was 15 s. In the intervals between the stimuli, a 10 s period of silence was inserted as a resting period. In the experimental session, the mother's voice stimulus and the stranger's voice stimulus were presented to

the neonates in random order. The experiment was finished when more than 5 trials of each stimulus condition succeeded without the presence of body movement artifacts. All neonates underwent this experiment in 6–10 min. Stimuli were presented to neonates with amplitudes of approximately 67 dB via two speakers positioned 45 cm away from the neonates' head.

The experiments were performed in a testing room at Keio University Hospital. We recorded the regional cerebral hemoglobin concentration changes using an optical topography system (ETG-4000, Hitachi Medical Corporation, Japan) while each participant lay face up on the bed and was exposed to the voice sound stimuli. The device used emitted light beams of 695 nm and 830 nm wavelengths. The maximum intensity of laser irradiation for each wavelength was 1.5 mW. The detected signal was sampled at 10 Hz and then transformed into oxygenated hemoglobin concentration changes (oxy-Hb) and deoxygenated hemoglobin concentration changes (deoxy-Hb) (mM•mm) according to the modified Beer-Lambert law. The oxy-Hb and deoxy-Hb were recorded at 46 locations by placing three silicon holders on the frontal region and left and right temporal regions of the participants' scalps. In each holder, the emitting and detecting probes were separated by 2 cm and arranged in 3 x 3 or 3 x 5 square lattice.

3. Analysis

The time-continuous data of oxy-Hb signals were separated into analysis blocks, which consisted of a 2 s pre-stimulation baseline period followed by 15 s stimulation period and 10 s post-stimulation baseline period. To eliminate long-term signal trends due to systemic vascular factors, a first-degree baseline fit was estimated for each channel using the first 2 s and last 2 s of each block. To investigate the latency property of the hemodynamic response associated with the recognition of the mother's voice, we calculated the latency of the maximum (and minimum) amplitude peak of the response curve for each block, for each channel. The latency data were traced into the histograms of 24 one-second-width bins. We considered the volume of each bin in the individual subject's histogram as random effects and performed a two-sample *t*-test between data for the mother's and the stranger's voice conditions with respect to each bin. This test was examined in order to determine the significant latencies that emerged more frequently in the mother's voice condition than in the stranger's voice condition, and vice versa. Note that

we removed the block data of trials affected by movement artifacts.

The resultant significant latencies were set as the value of delay in the hemodynamic response model calculated based on the fMRI response (Friston, et al., 1995), and different delay values were set in the models for term and preterm neonates. We examined the general linear model (GLM) analyses building these models into regressors. In the GLM method, Hb signal data were fitted by the weighted sum of each regressor of the hemodynamic response to each stimulus. The weights β_{mom} (for mother voice stimulus) and $\beta_{stranger}$ (for stranger voice stimulus) were calculated using the linear regression analysis for each group of neonates. The β values were entered into two-sample *t*-test in order to identify the channels where the activation associated with the mother's voice stimulus was significantly different from the activation associated with the stranger's voice stimulus. To take into account multiple comparisons among all channels, we applied the false discovery rate (FDR) procedure.

III. Results

For the reference, Figure 1 shows the averaged time courses of oxy-Hb block data for the mother's and stranger's voices. In both cases of term and preterm neonates, various types of response curves were observed over all channels. The peak of the response curve appeared immediately after the stimulus onset in some channels, and even after the stimulus offset in other channels (difference in the peak latency). The first peak had positive amplitude in some channels, while it had negative amplitude in other channels (difference in the peak polarity).

To determine what kind of peaks were more closely related to the mother's voice than the stranger's voice, we first found the positive peak of the maximum amplitude and the negative peak of the minimum amplitude in each block for each channel. After calculating the latency value for these peaks, the latency data distribution over all subjects was shown as a histogram of 1-s width bins (Figure 2). After normalizing the individual subject's histogram using kernel density estimation, we considered the individual density values as random effects and performed a two-sample t-test of the date for the mother's voice condition and that for the stranger's voice condi-

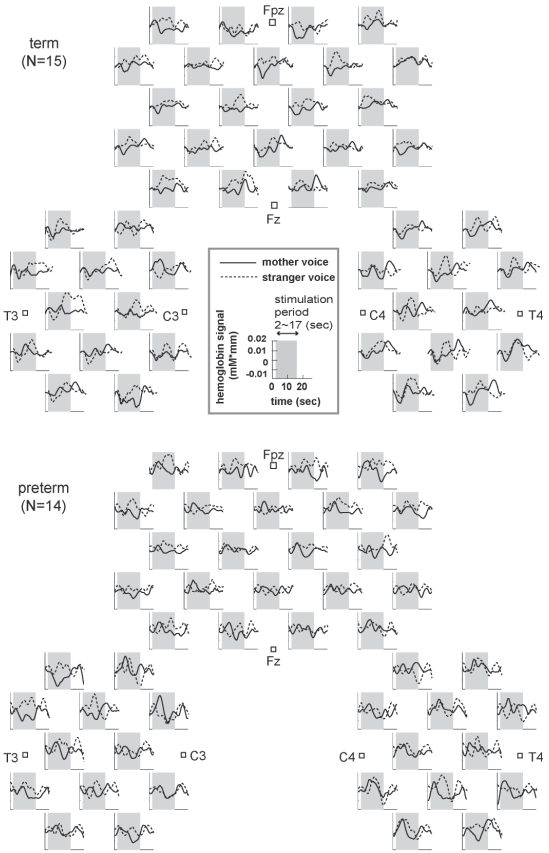

Figure 1. Grand averaged time courses of oxy-Hb to mother voice (solid line) and strange female voice (dashed line) for term and preterm neonates. Fpz, Fz, T3, T4, C3, and C4 indicate the reference positions on the scalp according to the international 10–20 method. The time zones in gray correspond to the period when voice stimulus was presented.

tion for each latency interval of 1-s width. In the case of term neonates, the significant peak latencies that emerged more frequently for the mother's voice stimuli than the stranger's voice stimuli were 21–23 s for positive peaks and 4, 5, 7, and 14 s for negative peaks. In the case of preterm neonates, the significant latencies were 6 s and 24 s for only positive peaks ($p < .05$). Based on these properties of peak latency and polarity, we set different hemodynamic response models for term and preterm neonates (Figure 3) and examined the GLM analyses using these models as regressors. The

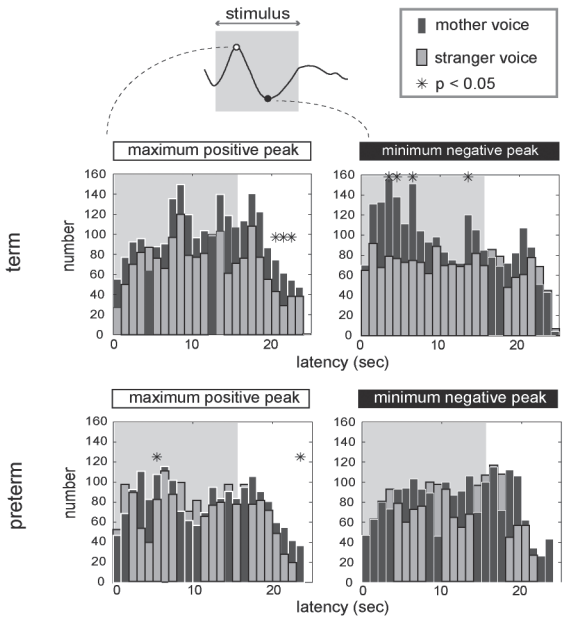

Figure 2. Histogram of peak latency data of oxy-Hb for term (upper side) and preterm (lower side) neonates. The histograms of the maximum positive peak latency data were shown in left side and the ones of the minimum negative peak latency data were shown in right side. Bins of the lower volume number stood forward, comparing between mother's and stranger's voice conditions. The vertical axis means the sum of latency data for all blocks for all channels. The dark gray bars indicate the number of the latency data to mother's voice and the light gray bars indicate that to stranger's voice. The mark of * indicates that the number of the latency data of the Hb signal was significantly different between mother's and stranger's voice conditions in the Hb signal having the latency with this mark (*t*-test, $p < .05$).

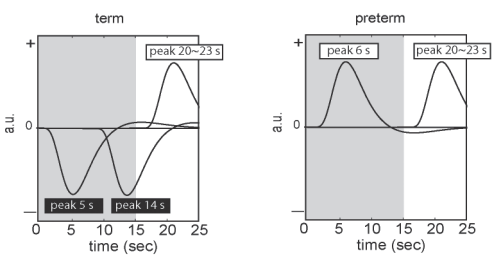

Figure 3. Scheme of the polarity and latency parameters of the hemodynamic response related to the mother's voice distinction from stranger's voice: term (left side) and preterm (right side). We examined GLM analyses shifting the hemodynamic response model by each of these latency values.

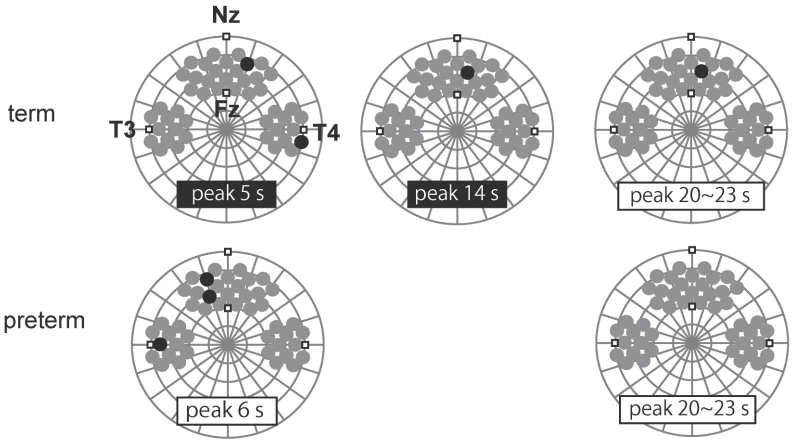

Figure 4. The spatiotemporal mappings of the greater response to the mother voice than the stranger voice for term (upper column) and preterm (lower column). In the channels in white, oxy-Hb response significantly more increased to mother's voice than to stranger's voice, and in the channels in black, oxy-Hb response significantly more decreased to mother's voice than to stranger's voice.

results are shown as spatiotemporal maps of mother-voice-specific responses in Figure 4. The responses of term neonates were right-hemisphere dominant, while the responses of preterm neonates were left-hemisphere dominant over all maps. Short latency responses of around 5 s after the stimulus onset appeared in the frontal area and the inferior temporal area, although the polarity feature was different between term and preterm neonates. Longer latency responses around 10 s and 20 s appeared in the frontal area (around the mid point of Fpz and Fz) only in term neonates.

IV. Discussion

We successfully detected rapid change in the cerebral hemodynamic concentration (oxy-Hb signal) induced by a mother's voice stimulus for term and preterm neonates. In the following discussion, we focused on several different features between term and preterm neonates' responses to their mother's voice.

First, why is the response to a mother's voice right-hemisphere dominant

in the case of term neonates, but left-hemisphere dominant in the case of preterm neonates? According to Dehaene-Lambertz et al. (2010), in the case of two-month old infants, the large blood oxygen level dependent (BOLD) response to a mother's voice appeared mainly in the left cortical areas (specifically the left and right anterior prefrontal cortex and the left posterior temporal region), while the large BOLD response to a stranger's voice appeared mainly in the right cortical areas (specifically the right and left orbitofrontal regions and the right anterior superior temporal sulcus and gyrus). From the standpoint of cerebral dominance, the spatial distribution of term neonates' responses to their mother's voice in this study was similar to that of two-month old infants' responses to a stranger's voice. However, the spatial distribution of preterm neonates' responses to their mother's voice in this study was similar to two-month old infants' responses to their mother's voice. This suggests that the cerebral hemodynamic responses to a mother's voice can reflect the number of days after birth rather than gestational age or postconceptional age.

Second, why was the polarity of the first peak response reversed for term and preterm neonates? The first peak of oxy-Hb response to the mother voice stimulus was negative and in the right cortical areas of term neonates, but for preterm neonates, it was positive and in the left cortical areas. Again, according to Dehaene-Lambertz et al. (2010), in the case of two-month old infants, negative BOLD responses to the mother voice stimulus appeared mainly in the right hemisphere (the right insula/amygdala/putamen, the right superior temporal sulcus). The response of term neonates in this study and the response of two-month old infants in the study of Dehaene-Lambertz were similar in terms of the negative response in the right hemisphere. The negative responses have been related to an immaturity of infants' neurovascular coupling, possibly associated with a higher demand in oxygen due to rapid synaptogenesis (Morita et al., 2000). An alternative interpretation is that the negative responses are related to a defensive neuronal activity, which might alleviate previous activities when the baby is distracted by suddenly hearing his or her mother. Moreover, another interpretation is that the negative responses were related to cardiac responses to a sound stimulus. According to Richards (1991), a decrease in the heart rate after hearing a sound reflects the attention-orienting mechanism. The negative response thus might be linked to the transmission of cardiac activity. Future studies are needed

in order to reveal the physiological meaning of this negative response, by analyzing the relationships between the cerebral hemodynamics and the cardiac responses to a sound.

Finally, why did a multiple-peaks response type of longer latencies appear in the frontal cortical area (around Fpz and Fz) of term neonates? Further, why was there no similar response in the preterm group? In the case of term neonates, the negative responses to the mother voice stimulus appeared at a latency of 14 s, while the positive response appeared at 20 s. Kubota et al. (2001) reported that frontal midline electroencephalography (around Fz) theta rhythms are associated with cardiac autonomic activities and motivation control. These longer latency responses are possibly related to a more sustained attention and motivation control, which is associated with heart rate acceleration appearing at longer latencies (Ramirez et al., 2005; Vila et al., 2007). However, it remains unclear whether the theta rhythms and the frontal hemodynamic responses are related to each other and are mediated by cardiac activity.

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