Frontal brain activation in premature infants' response to auditory stimuli in neonatal intensive care unit

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Abstract

The present study was focusing on the very few contacts with the mother's voice that NICU infants have in the womb as well as after birth, we examined whether they can discriminate between their mothers' utterances and those of female nurses in terms of the emotional bonding that is facilitated by prosodic utterances. Twenty-six premature infants were included in this study, and their cerebral blood flows were measured by near-infrared spectroscopy. They were exposed to auditory stimuli in the form of utterances made by their mothers and female nurses. A two (stimulus: mother and nurse)×two (recording site: right frontal area and left frontal area) analysis of variance (ANOVA) for these relative oxy-Hb values was conducted. The ANOVA showed a significant interaction between stimulus and recording site. The mother's and the nurse's voices were activated in the same way in the left frontal area, but showed different reactions in the right frontal area. We presume that the nurse's voice might become associated with pain and stress for premature infants. Our results showed that the premature infants reacted differently to the different voice stimuli. Therefore, we presume that both mothers' and nurses' voices represent positive stimuli for premature infants because both activate the frontal brain. Accordingly, we cannot explain our results only in terms of the state-dependent marker for infantile individual differences, but must also address the stressful trigger of nurses' voices for NICU infants.

1. Introduction

Many studies have shown that premature infants are at risk for emotional and behavioural problems. Some studies have reported problems such as inattention, impulsivity, hyperactivity, decreased adaptability, heightened intensity and higher thresholds to sensory stimuli [1–3], whilst others suggested that premature infants who showed lower scores on tests of cognitive functioning may be prone to having difficulties in behavioural adjustment [4], learning problems and poor academic achievement [5]. Accordingly, the optimal care of premature infants, especially with regard to mother–infant emotional bonding, plays an important role in children's subsequent develop ment and mental health.

In general, infants are known to accurately perceive multimodal stimuli in the first months of life [6]. Indeed, the auditory system is fully operative at the last trimester of gestation [7], so that infants already have about 12 weeks of auditory experience listening to sounds in the womb. Research has also indicated that infants can discriminate between sounds that they like and those they do not by birth [8]. Furthermore, it has been shown that infants like the higher pitched, sing-song style of speech often used by adults in speaking to infants, which is sometimes called “motherese” [9].

However, premature infants are often hospitalised in neonatal intensive care unit (NICU), which can disrupt the expected develop ment of interactive skills for both the parent and the infant [10]. The limitation on social interaction and physical contact required for infection prevention also makes mother–infant bonding difficult for infants in NICU. Accordingly, NICU infants have few opportunities to hear motherese, although they often hear a female nurse's voice having the rich intonation characteristic of motherese whilst they are being cared for in NICU.

Focusing on the very few contacts with the mother's voice that NICU infants have in the womb as well as after birth, we examined whether they can discriminate between their mothers' utterances and those of female nurses in terms of the emotional bonding that is facilitated by prosodic utterances.

Observing the slight overt responses characteristic of normal as well as premature infants is very difficult, and brain functions in premature infants are not yet fully understood. CaseyanddeHaan[11] pioneered a new direction for infant studies using new methods for brain imaging. These techniques are expected to enhance our understanding of infant perceptual abilities at the brain function level.

Following Caseyand deHaan[11], weintroducedthenear-infrared spectroscopy (NIRS) brain imaging technique into our study. The use of NIRS is advantageous in infant studies because linguistic or behav ioural skills are not required. Furthermore, NIRS techniques are robust and reliable for use with human infants [12]. Thus, focusing on changes in the frontal cerebral blood flow of premature infants, we examined how the infants responded to utterances by their real mothers and the female nurses caring for them.

2. Methods

2.1. Participants

Twenty-six Japanese infants (13 boys and 13 girls) ranging in age from 18 to 81 days (mean, 46.31 days; range, 35 weeks 6 days to 38weeks5dayspost-conceptionalage) participated in this study. The infants were born in 2006 and admitted at birth to Prefectural Hospital of Hiroshima (Hiroshima, Japan). The mean gestational age was 30.42 weeks (24 weeks 6 days to 35 weeks 4 days), and the average birth weight was 1385.42 g (602–2078 g). The infants were hospitalised, amongst other reasons, due to low birth weight (both very low birth weight and extremely low birth weight), respiratory distress syndrome (RDS), neonatal transient tachypnea and neonatal apneic attack. No neurological disorders were identified by neuro logist diagnosis. The infants' auditory ability was also assessed as normal by means of an automated auditory brain stem response in hospital. When the infants recovered sufficiently to breathe sponta neously, they were moved from NICU to the growing care unit (GCU). This study was endorsed by the ethics committee of Prefectural Hospital of Hiroshima. All parents received and understood the relevant research information and signed an informed consent form.

2.2. Stimuli and apparatus

Stimuli for each infant consisted of the mother's voice and a female nurse's voice, both in Japanese. Each mother was allowed to interact with her baby only for 3 h during the 11.5-h period designated as visiting hours bythe hospital. Althoughit was rarefora mothertovisit her baby daily, the charge nurse was with the infants for approxi mately 8 h every day.

We recorded speech samples from each mother whose infants participated in the experiment and from the nurse in charge of the infants. The recorded sample was an utterance such as “Good morning, it's time to have your milk” (in Japanese, “Ohayo, Milk-no Jikan-desu-yo”). Before their utterances were recorded, the women were instructed to speak to the infant as they usually would. The speech elements involved in the two versions differed between speakers with respect to total duration, tone intensity, speaking speed, volume and pause duration.

Watterson and Riccillo [13] found that white noise is particularly effective in soothing crying infants. Accordingly, in our study, computer generated white noise was used as a control auditory stimulus during the baseline oxygenation levels before presenting the mother's voice or the nurse's voice, as well as during a relaxation period after stimulus exposure. All auditory stimuli were recorded by a stereo digital voice recorder (ICR-S300RM; Sanyo K.K., Osaka,Japan) and formatted asMP3 files.

2.3. NIRS recording

Changes in oxygenated haemoglobin (oxy-Hb), deoxygenated haemoglobin (deoxy-Hb) and total haemoglobin (total-Hb) in blood from the frontal area of the brain were detected using the double channels of a near-infrared oxygenation monitoring device (NIRO 200; HamamatsuPhotonicsK.K.,Hamamatsu,Japan).Using safe, faint, near-infrared light, we measured the tissue oxygenation index (TOI) for the oxygen saturation level and the normalised tissue haemoglo bin index (nTHI) for the blood concentration, as well as for changes in the concentration of oxy-Hb, deoxy-Hb and total-Hb in real time. Near-infrared light with a wavelength of approximately 700–950 nm can pass through body tissue relatively well. The absorption can vary according to the oxygenation condition of the haemoglobin, but the main advantage of NIRS is that it allows the non invasive measurement of the oxygenation levels of deep tissue in the brain as well as the oxygen concentration levels in the blood. Changes in the concentrations of oxy-Hb, deoxy-Hb and total-Hb were calculated with respect to the time changes in light attenuation at the measurement location. A personal computer converted the absorption changes at each wavelength, recorded every 1/6 s, into relative concentration changes in cerebral chromophores. The changes were expressed in micromoles per litre. To detect the tissue oxygenation with the NIRO-200, we used a probe designed for infants that consisted of an emission and a detection site with a 3-cm interoptode distance. For infants, the optical path length of the probe could be estimated by multiplying the interoptode distance by a 3.9 path-length differential factor [14].

2.4. Procedure

The infants were tested in their cribs whilst they slept in a silent room. Their sleep state was STATE 1-2 (not arousal) according to our observation based on Brazelton's scale. The temperature and light intensity of the room were kept constant, and the noise level was reduced as much as possible. First, two probe holders were placed on the left and right sides of the forehead over the eyebrows, which corresponded to an Fp1 or an Fp2 placement of a 10/20 EEG system, using double-sided adhesive tape. To prevent ambient light from reaching the optode, dark felt was bandaged over the infant's head. After fitting the optode sets on the forehead, a few minutes were required to check whether the sensors were making good contact. The experimenter did not touch or talk to the infant during the test. Each infant was then exposed to the auditory stimuli in the form of the mother's voice, the nurse's voice or white noise through an external auditory speaker (Acoustic Bass Duct; Sony, Tokyo, Japan) placed 10 cm away from the infant's face (through a portable storage device and multi-code jukebox with 64-kbit rates). The speaker sound had a 60–70-dB sound-pressure level (SPL) as measured with a sound-level meter (NL-05A; Rion, Tokyo, Japan).

The test was divided into two blocks and repeated four times. The order of presentation of the auditory stimuli was counterbalanced between participants. Each block consisted of three presentations of voice stimulation made repeatedly over 10 s. In the intervals between blocks, white noise was presented for 20s.TheNIRO-200 was triggered by “on” and “off” signals when the infants were exposed to auditory stimuli, and oxygenation levels in the blood were scanned during the test. The total procedure, including the placement of probes, took approximately 10 min.

2.5. Data análisis

We focused our analyses on changes in oxy-Hb because it is believed to be the most sensitive indicator of changes in cerebral blood flow for NIRS measurements [15]. We collected 2280 oxy-Hb data per participant. However, as body movementsmayalso influence oxy-Hb data value, we excluded data that were over 2 standard deviations (SDs) from the mean for each participant. NIRS studies have also revealed slow oscillations of the haemoglobin oxygenation state in infants [16]. Therefore, to correct for slow oscillations and instability of the baselines, we took a fitting using a linear function and calculated the analogue data. The oxy-Hbvalue measured by NIRS is a relative value compared to a baseline rather than an absolute value. Accordingly, we treated the quantity of change for each item as an interval scale value by calculating a value for the difference in oxy-Hb 5safter a stimulus presentation began compared tothevalue5sprior to onset of the stimulus.

3. Results

We used the differences between white noise and relative stim ulation values in the following statistical analyses. The means of the two different stimuli were calculated separately for each infant (Table 1).

We conducted a 2 (stimulus: mother and nurse)×2 (recording site: right frontal area and left frontal area) analysis of variance (ANOVA) for these relative oxy-Hb values. The ANOVA showed a significant interaction ($F(1, 25)=6.181$, pb0.05) between stimulus and recording site (Fig. 1). Post hoc analyses (Ryan's methods) indicated a tendency for the nurse's voice to produce a greater increase of oxygenated blood than the mother's voice at the right frontal recording site ($F(1, 50)=3.025$, pb0.10). In other words, the mother's and the nurse's voices were activated in the same way in the left frontal area, but showed different reactions in the right frontal area. That is, the right frontal area appears not to have been activated by the mother's voice, although activation did occur in response to the nurse's voice.

4. Discussion

We investigated the effect of language stimulation on frontal brain activation in premature infants in NICU using two different utterance conditions: mothers' and nurses' voices.

Fig. 1 suggests that the frontal area was activated approximately equally by the mother's and the nurse's utterances. Our previous research showed that prosodic utterance can activate the frontal area of the infant's brain [17,18]. With respect to Japanese full-term neonates ranging in age from 2 to 9 days, it was shown not only that the mother's prosodic utterance and infant-directed speech significantly activated the frontal cerebral blood flow at sites on both sides of the infant's brain [17], but also that prosodic infant-directed speech on the frontal cerebral blood flow was significantly more effective in this regard compared to monotonous utterance or adult-directed speech [18].

The findings from that earlier study suggested that prosodic patterns, such as the mother's utterances, can activate the infant's brain. However, although those full-term neonates were able to discriminate prosodic utterances, we were unable to determine whether they were able to recognize them as their mothers' speech. Accordingly, such utterances may have been effective for full-term neonates in terms of arousal stimulation rather than verbal stimulation. Moreover, our results suggested that the emotional tone of maternal utterances may play a role in activating the neonate's brain. If this was true, it may be that the mother–infant emotional bond associated with the mother's voice might induce activity in the frontal area.

Cosmides [19] stressed that consistent acoustic configurations of emotional expressions could yield important information about the speaker's intention and motivation. From his point of view, our pre sent result may suggest that premature infants could perceive the speaker's emotional tone on the basis of the prosodic features of the voice stimuli. Moreover, this may be closely related to adults' frequent use of infant-directed speech (i.e., motherese) with infants, in contrast to their adult-directed speech. Accordingly, as mothers and nurses may be perceived as the same for premature infants with respect to the care they provide, these infants would be expected to respond to the same tone whether it came from the mother or the nurse.

The statistically significant interaction between the stimulus (mother vs. nurse voice) and the recording site revealed that the mother's voice activated the left frontal area more than it did the right, whereas the nurse's voice activated the right frontal area more than it did the left. Moreover, the results indicated that the nurse's voice, but not the mother's, activated both frontal areas. Generally, language stimuli are accepted to activate the left hemisphere more so than the right, and this phenomenon may explain the asymmetric result for the mother's voice. However, the response to the nurse's voice was not consistent with the presumed hemispheric asymmetry for language stimuli. Accordingly, we propose an explanation for this finding in terms of the function served by the nurse's voice for premature infants.

The explanation assumes that the nurse's voice might provide positive stimulation for the right hemispheric functions in premature infants. For example, a fMRI study showed right hemispheric activation in response to an utterance with emotional intonation in full-term neonates [20]. Moreover, an EEG study by Dawson and Ashman [21] showed reduced activation in the right hemisphere of infants' brains when they played “peek-a-boo” with mothers who were depressed. Of particular importance here is that the latter result was explained in terms of a developmental malfunction, in which the right hemispheric function in the infants could not be activated because of their long term exposure to the non-animated expressions of their depressed mothers. This conclusion may explain the frontal activation asymmetry found in the present study in terms of Dawson and Ashman's [21] notion of a state-independent marker for individual differences in the threshold of reactivity to stressful events as well as in vulnerability to particular emotions.

These two studies on right hemispheric function in infants suggest that even in early developmental stages, infants' brains can process language stimuli as expressions of others' emotional status. Accordingly, we presume that the nurse's voice may serve the function of providing speech that carries emotional intonation for NICU infants.

In contrast, some research has found an absence of right hemi spheric activation in some infants. An EEG study showed that crying infants who had experienced maternal separation showed greater activation in the right frontal area during the baseline period than infants who were not crying[22].This result was explained in terms of a state-independent marker for individual differences in the threshold of reactivity to stressful events as well as in vulnerability to particular emotions. According to this result, the right frontal activity in our premature infants in response to the nurse's voice can be explained on the basis of their weak reactivity and vulnerability to stress due to maternal deprivation.

Premature infants in NICU have already undergone stressful and painful procedures such as injections and tests. For example, Yamada et al. [23] found no significant differences between the hair cortisol levels of term infants compared to preterm infants in NICU, whereas hospitalised infants had significantly higher hair cortisol levels compared to non-hospitalised infants. Moreover, a correlation was found between the total number of days that infants were on a ventilator and hair cortisol levels. Thus, premature infants in NICU experience chronic neonatal stress. Furthermore, their brains, and therefore their cognitive development, are also affected by these stresses. Likewise, neonatal stress increases cortisol levels, and heightened cortisol has been shown by EEG to result in increased right prefrontal activity during a withdrawal–negative affect task associated with fear and sadness [24].

On the basis of these findings, we presume that the nurse's voice might become associated with pain and stress for premature infants. Our results showed that the premature infants reacted differently to the different voice stimuli. Therefore, we presume that both mothers' and nurses' voices represent positive stimuli for premature infants because both activate the frontal brain. Accordingly, we cannot explain our results only in terms of the state-dependent marker for infantile individual differences, but must also address the stressful trigger of nurses' voices for NICU infants