Effect of therapeutic touch on brain activation of preterm infants in response to sensory punctate stimulus: a near-infrared spectroscopy-based study

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ABSTRACT
Objective The purpose of this study was to determine whether therapeutic touch in preterm infants can ameliorate their sensory punctate stimulus response in terms of brain activation measured by near-infrared spectroscopy.

Methods The study included 10 preterm infants at 34–40 weeks’ corrected age. Oxyhaemoglobin (Oxy-Hb) concentration, heart rate (HR), arterial oxygen saturation (SaO2) and body movements were recorded during low-intensity sensory punctate stimulation for 1 s with and without therapeutic touch by a neonatal development specialist nurse. Each stimulation was followed by a resting phase of 30 s. All measurements were performed with the infants asleep in the prone position.

Results sensory punctate stimulus exposure significantly increased the oxy-Hb concentration but did not affect HR, SaO2 and body movements. The infants receiving therapeutic touch had significantly decreased oxy-Hb concentrations over time.

Conclusions Therapeutic touch in preterm infants can ameliorate their sensory punctate stimulus response in terms of brain activation, indicated by increased cerebral oxygenation. Therefore, therapeutic touch may have a protective effect on the autoregulation of cerebral blood flow during sensory punctate stimulus in neonates.

INTRODUCTION
Hospitalised preterm infants have physiologically immature systems, low tactile threshold and heightened responses to stimuli, at a time when they may be subjected to repeated invasive and painful procedures.1 2 Recurring and sustained pain exposure in the perinatal period is associated with long-term neurological, social and cognitive developmental sequelae.3–5 However, control of pain in preterm infants improves their clinical stability and ameliorates medical complications.6 Non-pharmacological pain management in infants has an evidently favourable effect on pulse rate, respiration, oxygen saturation, motor activity and regulation of excitation states after invasive measures.7 For example, skin-to-skin contact,8 facilitated tucking9 and holding10 are effective in alleviating pain in neonates.

Painful and distressing events can cause disturbances in cerebral oxygenation.11 In this context, near-infrared spectroscopy (NIRS) is a feasible method to detect variations in hemodynamic responses to sensory stimulation; it has been used to investigate cortical processing following painful stimulation in preterm infants.12–16 Slater et al15 ascertained that noxious information is transmitted to the preterm infant cortex from 35 weeks, highlighting the potential for both higher-level pain processing and pain-induced plasticity in the human brain from an early age. Further, Bartocci et al16 suggested that painful tactile stimuli elicit specific hemodynamic responses in the somatosensory cortex, implying that sensory perception in preterm neonates is a conscious process. Moreover, pain-related cortical activation is inversely correlated with gestational age, and positively correlated with postnatal age. Since it would not be ethical to inflict pain for a purely research purpose, this NIRS-based study aimed to determine whether therapeutic touch in preterm infants can ameliorate the brain activation response to a sensory punctate stimulus.

METHODS
Subjects
The study included 10 preterm infants (five girls and five boys). The inclusion criteria were absence of congenital heart disease, abnormal central nervous system manifestations, chromosomal aberrations and lung malformations. The infants were cared for in the neonatal intensive care unit of Kinki University Hospital between Jun 2009 and
July 2010. Their parents gave written informed consent, and the Ethics Committees of Seirei Christopher University (approval No. 09023) and Kinki University Hospital (approval No. 20-39) approved the study.

**Study design and experimental tasks**

Design of the study was cross-sectional. The study was divided into two experimental tasks: task 1, sensory punctate stimulus without therapeutic touch, and task 2, sensory punctate stimulus with therapeutic touch. Each task included a baseline period of at least 10 s, low-intensity punctate stimulus for 1 s, and a resting phase of 30 s (figure 1A). The tasks were conducted with the infants asleep (behavioural state 17) in the prone position with the head turned to the left at least 30 min after feeding. The infants slept in a dark, quiet room during the experiment. The infants were monitored by NIRS, heart rate (HR) and arterial oxygen saturation (SaO₂) recordings during the tasks.

**Low-intensity punctate stimulus**

For sensory punctate stimulus, a standardised instrument designed for sensory quantitative pain testing (Quantitaive esthesiometer, Yufuseiki Co Ltd, Tokyo, Japan) was used. The stimuli were randomly applied to the infants’ right or left heel at an intensity of 10 g. In the pilot testing, this intensity had no effect on the infants’ state change, HR, SpO₂, and motor behaviour.

**Therapeutic touch intervention**

Therapeutic touch involved facilitated tucking (containment) of each infant’s whole body by a neonatal development specialist nurse using both hands from 1 min before to 30 s after the stimulation. For containment, the infants were maintained in the prone position with their extremities flexed and close to the trunk. They were enwrapped by the nurse’s hands and touched gently with the palms of both hands (right hand placed on the upper body and left hand placed on the lower back and hip).

**Measurement of brain activation**

The relative changes in oxyhaemoglobin (oxy-Hb) and deoxy-Hb concentrations were measured with an NIRS instrument (ETG-7100, Hitachi Medical Corporation, Tokyo, Japan) with multiple channels, 0.1 s resolution and 2 wavelengths of near-infrared light (780 and 830 nm). Data analyses were based on the modified Lambert-Beer law. During cortical activity, a neurovascular process occurs whereby changes occur in cerebral blood flow, volume and metabolic rate of oxygen consumption. Because the precise optical path length was unknown, the unit of measurement used was molar concentration multiplied by length (mM mm). Detailed descriptions of the principles underlying NIRS have been published previously. The rationale for this approach rests on the concept that neural activation in response to a stimulus results in increased energy demands in the area activated. In response to this demand, cerebral blood flow increases to the activated regions. Changes in blood flow lead to an increase in blood volume and can be assessed by measuring local concentrations of oxy-Hb and deoxy-Hb.

We used one 4×4 arrayed probe mounted on a flexible cap, which was placed over the somatosensory cortex at Cz, C3, and C4, based on the International 10–20 system for recording EEG. The distance between the emitting and the detecting fibres was 2 cm. Each pair of adjacent emitting and detecting fibres defined a single measurement channel, allowing the measurements of oxy-Hb and deoxy-Hb concentrations in 24 channels. Oxy-Hb concentrations were calculated from two areas to measure the effects of low-intensity punctate stimulation: contralateral somatosensory region (CSR) and ipsilateral somatosensory region (ISR).
somatosensory region (figure 1B). The time courses of and average task-related changes in oxy-Hb signals from the baseline were calculated.

Measurement of HR and SaO2
HR and SaO2 were recorded with a pulse oximeter (OxiMax N-600x; Covidien-Nellcor, Boulder, Colorado, USA) simultaneously with the NIRS data, and analysed by a data acquisition and analysis system (MP system; BIOPAC Systems, Inc, Goleta, California, USA) at a sampling rate of 10 Hz. The values were averaged at the baseline and throughout each task.

Statistical analysis
A paired t-test was used for statistical comparisons of the time courses of oxy-Hb concentrations and HR and SaO2 data between the tasks. All statistical analyses were performed with SPSS V.18.0J for Windows (IBM-SPSS Japan, Tokyo, Japan).

RESULTS
Subject characteristics
Table 1 shows the subject characteristics. The infants were born at 28–33 weeks’ gestation, and their mean (SD) birth weight was 1277 (344) g. Their mean (SD) Apgar scores were 7.3 (1.8) at 1 min and 8.9 (0.9) at 5 min. The experimental procedures were conducted when the infants reached 11–66 days’ postnatal age, or 34–40 weeks’ corrected age. Their mean (SD) body weight at the time of the study was 1989 (314) g. The mean (SD) duration on mechanical ventilation was 3.8 (7.2) days. The infants underwent 17.7 (5.7) venipunctures and 20.0 (19.3) heel lances. There were no participants with missing data for outcome variables.

Table 1 Details of the subjects (n=10)

| Age, or 34 | Gestational age at birth (weeks) | 29.4 (1.5), 28–33 |
| Birth weight (g) | 1277 (344), 974–2218 |
| Male/female (n) | 5/5 |
| Vaginal delivery (n) | 0 |
| Appar score at 1 min | 7.3 (1.8), 4–9 |
| Appar score at 5 min | 8.9 (0.9), 7–10 |
| Postnatal age (days) | 47 (19), 11–66 |
| Corrected age (weeks) | 36.2 (2.1), 34–40 |
| Weight during study (g) | 1989 (314), 1610–2440 |
| Duration of mechanical ventilation (days) | 3.8 (7.2), 0–24 |
| Number of venipunctures | 17.7 (5.7), 8–25 |
| Number of heel lances | 20.0 (19.3), 2–60 |

Data represent means (SD) and ranges, unless indicated otherwise.

HR, SaO2 and oxy-Hb data
Figure 1 shows the mean values of HR and SaO2 at the baseline and during the tasks. During the tasks, no significant changes in HR and SaO2 were noted.

Figure 2 shows the time courses of the average oxy-Hb concentrations during the tasks, which were calculated from the baseline in each task. The CSR had significantly decreased oxy-Hb concentration during 12–21 s in task 2 compared with task 1 (p<0.05) (figure 3).

DISCUSSION
In this study, we found that therapeutic touch is effective in decreasing response to sensory punctate stimulus as reflected by changes in brain activation. Here, we demonstrate the possibility that therapeutic touch can reduce excessive brain activity induced by sensory punctate stimulus. The intensity of sensory punctate stimulation used in this study was lower compared with the clinical pain exposure typically experienced by neonates in the newborn intensive care unit (NICU). However, it would not be ethical to inflict pain for a purely research purpose. The sensory punctate stimulation successfully induced brain activation, and therapeutic touch decreased this brain activation.

In this study, the oxy-Hb concentration significantly increased after the sensory punctate stimulus, without changes in HR, SaO2 and body movements. Using NIRS, Slater et al indicated that noxious stimulation evokes specific hemodynamic changes in the cortex of the infants at 35 weeks’ premenstrual age,22 and painful stimuli elicit specific hemodynamic responses in the contralateral somatosensory cortex following unilateral stimulation.13 Our results are consistent with their findings. Increase in HR and hemodynamic changes in response to acute pain exposure (eg, venipuncture) can affect cerebral perfusion and oxygenation in the somatosensory areas, detected by NIRS. Kusaka et al23 evidenced a positive relationship between cerebral blood flow and cardiac output in infants. Previous studies compared non-activated areas, thereby eliminating the effects of global perfusion changes.15,16 Our results clarify that sensory punctate stimulus elicits cerebral blood flow changes without global increases in perfusion and cardiac output secondary to the sensory punctate stimulus intensity. Further, Slater et al22,24 suggested that pain may be processed at the cortical level without producing detectable behavioural or physiological changes, although noxious stimulation generally evokes parallel cortical and behavioural responses in infants. True experience of pain must involve supraspinal processing, and noxious information transmitted to the immature cortex of preterm infants can affect higher levels of the central nervous system. Our findings support the notion that pain is experienced even when motor and physiological responses to pain are not observed.

Figure 2 Changes in heart rate (HR, A) and arterial oxygen saturation (SaO2, B). The baseline was a period of at least 10 s before the stimulation (●); tasks 1 and 2 were punctate stimulation for 1 s without (●) and with (×) therapeutic touch, respectively. Data represent means (SE) of 10 subjects.
In this study, we found significantly lower oxy-Hb concentrations in the CSR during task 2 than during task 1. This result shows that therapeutic touch is effective in decreasing sensory punctate stimulus response, as reflected by changes in brain activation. However, this study was designed specifically to examine whether neural activity is associated with sensory punctate stimulus that does not trigger observable body movement, and avoids confounding factors because of cerebral perfusion which will be changed by cardiovascular responses.

In conclusion, our study demonstrated increased neural activation in the CSR following unilateral, low-intensity sensory punctate stimulation in preterm infants. Therapeutic touch modified the changes of cerebral oxygenation in response to sensory punctate stimulus. These findings support the accumulating evidence that modulating pain responses in the neonatal period has implications for brain development and plasticity. Therapeutic touch, as applied in the NICU, may have a protective effect on the autoregulation of cerebral blood flow during pain exposure in neonates.

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