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

Noritsugu Honda,[1,2] Shohei Ohgi,[2] Norihisa Wada,[3] Kek Khee Loo,[4] Yuji Higashimoto,[5] Kanji Fukuda[1]

[1]Department of Rehabilitation, Kinki University Faculty of Medicine, Osakasayama, Osaka, Japan
[2]Graduate School of Rehabilitation and Health Sciences, Seirei Christopher University, Hamamatsu, Shizuoka, Japan
[3]Department of Pediatrics, Kinki University Faculty of Medicine, Osakasayama, Osaka, Japan
[4]Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[5]Department of Respiratory Medicine and Allergology, Kinki University Faculty of Medicine, Osakasayama, Osaka, Japan

Correspondence to
Noritsugu Honda, Department of Rehabilitation, Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osakasayama, Osaka 589-8511, Japan; noritsugu.honda@sayama.med.kindai.ac.jp

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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 (SaO_2) 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, SaO_2 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.

What is already known on this topic

- The non-invasive near-infrared spectroscopy technique has been used to research neonatal brain activation induced by sensory punctate stimulation. In preterm neonates, sensory punctate stimulus elicits specific hemodynamic responses in the somatosensory cortex.

What this study adds

- The oxyhaemoglobin concentration significantly increased after the low-intensity sensory punctate stimulus, without changes in heart rate, SaO_2 and body movements.
- Therapeutic touch in preterm infants can ameliorate their sensory punctate stimulus response in terms of brain activation.

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 tucking[9] and holding[10] 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 al*[15] 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 al*[16] 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 1[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 (SaO_2) 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, SpO_2, 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.[7 18] 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.[19] 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.[20 21] 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

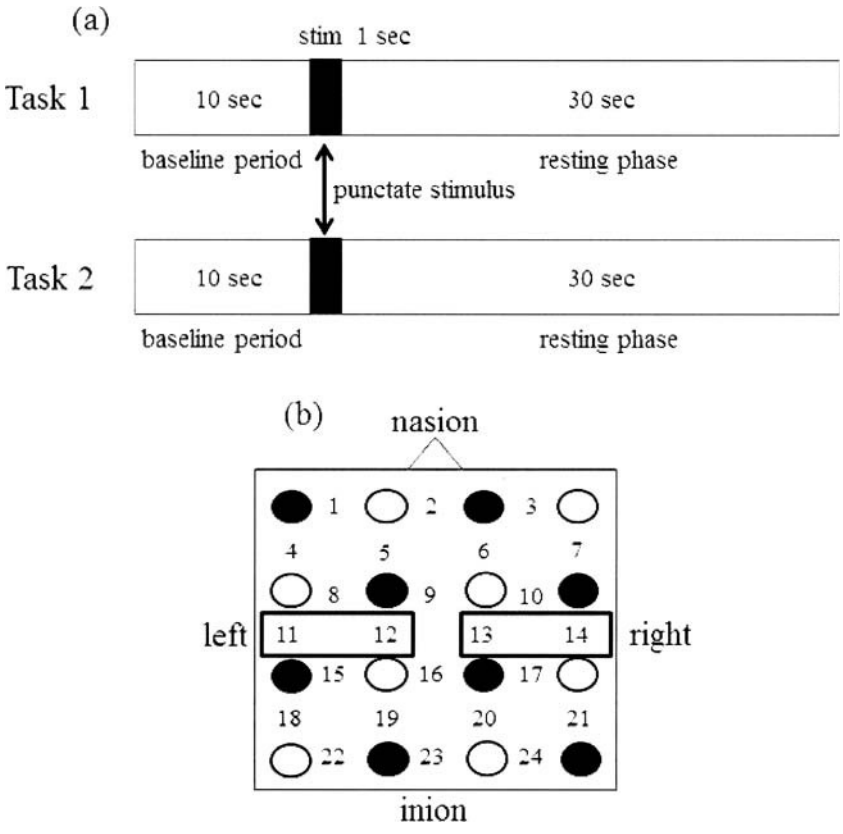

Figure 1 (A) Task 1: punctate stimulation without therapeutic touch. Task 2: punctate stimulation with therapeutic touch. Time schedule for measuring optical topographic data. After 10 s baseline period, punctate stimulation was added followed by 30 s resting phase. (B) Near-infrared light with wavelengths of 780 and 830 nm was guided by optical fibre bundles and transmitted into the cranium. The reflection of the infrared light (black) was sampled by receiving probes (number) placed on the scalp 2 cm away from the transmitting probe (white) and was detected with silicon photodiodes. The regions of interest (ROIs) were determined on the left hemisphere (channels 11 and 12) and right hemisphere (channels 13 and 14) (squares).

Table 1 Details of the subjects (n=10)

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
Apgar score at 1 min	7.3 (1.8), 4–9
Apgar 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 lancings	20.0 (19.3), 2–60

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

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 SaO_2

HR and SaO_2 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 SaO_2 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 (1.9) 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 (5.8) venipunctures and 20.0 (19.3) heel lances. There were no participants with missing data for outcome variables.

HR, SaO_2 and oxy-Hb data

Figure 1 shows the mean values of HR and SaO_2 at the baseline and during the tasks. During the tasks, no significant changes in HR and SaO_2 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, SaO_2 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.[15] 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 al*[23] 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 al*[22 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.

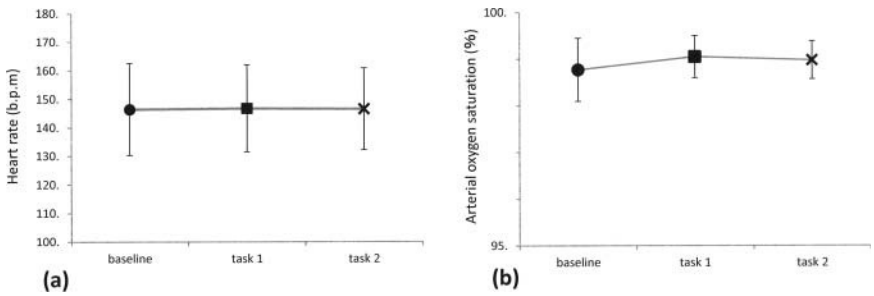

Figure 2 Changes in heart rate (HR, A) and arterial oxygen saturation (SaO_2, B). The baseline was a period of at least 10 s before the stimulation (•); tasks 1 and 2 were punctate stimulation for 1 s without (■) and with (×) therapeutic touch, respectively. Data represent means (SE) of 10 subjects.

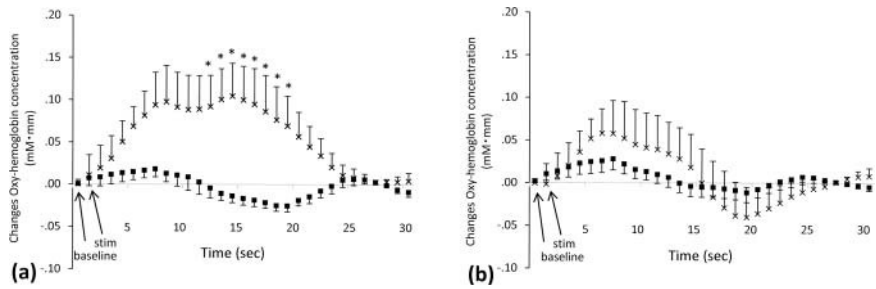

Figure 3 Time courses of oxyhaemoglobin concentrations after stimulation in the contralateral (A) and ipsilateral (B) somatosensory regions (average of 4 channels). Tasks 1 and 2 were punctate stimulation for 1 s with (■) and without (×) therapeutic touch, respectively. Data represent means (SE) of 10 subjects; *p<0.05.

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. Rather, therapeutic touch has a role in decreasing the cortical response to sensory punctate stimulus. As the mechanism underlying the effect of therapeutic touch, multiple factors may exist. One possible explanation is the gate control theory of pain that offers a neurological mechanism for pain reduction by therapeutic touch.[25] Melzack and Wall proposed that gating mechanisms exist within the dorsal horn of the spinal cord, and the interactions between local and distant excitatory and inhibitory systems in the dorsal horn and brain determine when painful stimuli reach the cortical level. In addition, pain is produced in a widely distributed neural network consisting of loops between the thalamus and the cortex, as well as between the cortex and the limbic system. Therefore, therapeutic touch may activate a non-nociceptive tactile nerve impulse (large nerve fibres), closing the gate in the dorsal horn, inhibiting nociceptive transmission, and subsequently reducing responses in the neural network of the brain and the pain experience. Another possible mechanism of analgesia is the release of oxytocin in response to skin-to-skin contact.[26] Oxytocin is a hormone produced by the hypothalamus in response to pleasant sensory stimulation, and might be released in neonates when in skin-to-skin contact. Most studies about tactile stimulation suggest that preterm infants who receive touch care derive benefits based on physiological and behavioural responses which are associated with improved developmental outcomes in these infants.[27 28] This study contributes to the literature by documenting the changes in brain activation in response to sensory punctate stimulus during therapeutic touch in preterm infants.

Fabrizi *et al*[29] reported that cortical activations of infants by pain and touch were discriminated by EEG response. However, we cannot determine whether the punctate sensory stimulus used in this study was that of pain or touch for infants, because temporal resolution of NIRS is not as good as EEG.

This study has several limitations. The sample size was small and the gestational age range was wide. Further, Bartocci *et al*[16] suggested that responses to pain are greater in preterm boys than in girls, and noted a negative correlation between pain-induced cortical activity and gestational age, as well as an increase in pain response with postnatal age. Our sample size was inadequate to evaluate the effects of gender and differences based on gestational and postnatal ages. Longitudinal effects of pain exposure and modulation by therapeutic touch need to be assessed in future studies. Moreover, the intensity of sensory punctate stimulation used in this study was lower compared with the clinical pain exposure (eg, from venipuncture and heel lancing) typically experienced by neonates in the NICU. Further studies should include comparison with measurements obtained under clinical conditions of pain exposure in the NICU. 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.

Contributors NH carried out all measurement and wrote the manuscript. SO and KKL thought about the analysis method of data. NW explained a study method to parents and obtained their consent. YH and SO helped with a measurement and the analysis of data. KF designed the projected and edited the manuscript. All authors contributed to regular discussion on the design and interpretation of the studies.

Competing interests None.

Patient consent Obtained from parents.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bouza H. The impact of pain in the immature brain. *J Matern Fetal Neonatal Med* 2009;22:722–32.
2 Grunau RE, Holsti L, Peters JW. Long-term consequences of pain in human neonates. *Semin Fetal Neonatal Med* 2006;11:268–75.
3 Abdulkader HM, Freer Y, Garry EM, *et al*. Prematurity and neonatal noxious events exert lasting effects on infant pain behaviour. *Early Hum Dev* 2008;84:351–5.
4 Anand KJ, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonate* 2000;77:69–82.
5 Oberlander TF, Grunau RE, Whitfield MF, *et al*. Biobehavioral pain responses in former extremely low birth weight infants at four months' corrected age. *Pediatrics* 2000;105:e6.
6 Anand KJ. Clinical importance of pain and stress in preterm neonates. *Biol Neonate* 1998;73:1–9.
7 Cignacco E, Hamers JP, Stoffel L, *et al*. The efficacy of non-pharmacological interventions in the management of procedural pain in preterm and term neonates. A systematic literature review. *Eur J Pain* 2007;11:139–52.
8 Gray L, Watt L, Blass EM. Skin-to-skin contact is analgesic in healthy newborns. *Pediatrics* 2000;105:e14.
9 Ward-Larson C, Horn RA, Gosnell F. The efficacy of facilitated tucking for relieving procedural pain of endotracheal suctioning in very low birthweight infants. *MCN Am J Matern Child Nurs* 2004;29:151–6; quiz 7–8.
10 Gormally S, Barr RG, Wertheim L, *et al*. Contact and nutrient caregiving effects on newborn infant pain responses. *Dev Med Child Neurol* 2001;43:28–38.
11 Gagnon RE, Leung A, Macnab AJ. Variations in regional cerebral blood volume in neonates associated with nursery care events. *Am J Perinatol* 1999;16:7–11.
12 Bartocci M, Winberg J, Papendieck G, *et al*. Cerebral hemodynamic response to unpleasant odors in the preterm newborn measured by near-infrared spectroscopy. *Pediatr Res* 2001;50:324–30.
13 Meek JH, Firbank M, Elwell CE, *et al*. Regional hemodynamic responses to visual stimulation in awake infants. *Pediatr Res* 1998;43:840–3.
14 Zaramella P, Freato F, Amigoni A, *et al*. Brain auditory activation measured by near-infrared spectroscopy (NIRS) in neonates. *Pediatr Res* 2001;49:213–19.

15 Slater R, Cantarella A, Gallella S, *et al*. Cortical pain responses in human infants. *J Neurosci* 2006;26:3662–6.
16 Bartocci M, Bergqvist LL, Lagercrantz H, *et al*. Pain activates cortical areas in the preterm newborn brain. *Pain* 2006;122:109–17.
17 Brazelton TBNK. *Neonatal behavioral assessment scale*. 3rd edn. London: Mac Keith Press, 1995.
18 Stevens B, Gibbins S, Franck LS. Treatment of pain in the neonatal intensive care unit. *Pediatr Clin North Am* 2000;47:633–50.
19 Villringer A, Chance B. Non-invasive optical spectroscopy and imaging of human brain function. *Trends Neurosci* 1997;20:435–42.
20 Gervain J, Macagno F, Cogoi S, *et al*. The neonate brain detects speech structure. *Proc Natl Acad Sci USA* 2008;105:14222–7.
21 Kobayashi E, Kusaka T, Karaki M, *et al*. Functional optical hemodynamic imaging of the olfactory cortex. *Laryngoscope* 2007;117:541–6.
22 Slater R, Fitzgerald M, Meek J. Can cortical responses following noxious stimulation inform us about pain processing in neonates? *Semin Perinatol* 2007;31:298–302.
23 Kusaka T, Okubo K, Nagano K, *et al*. Cerebral distribution of cardiac output in newborn infants. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F77–8.
24 Slater R, Cantarella A, Franck L, *et al*. How well do clinical pain assessment tools reflect pain in infants? *PLoS Med* 2008;5:e129.
25 Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971–9.
26 Hurst NM, Valentine CJ, Renfro L, *et al*. Skin-to-skin holding in the neonatal intensive care unit influences maternal milk volume. *J Perinatol* 1997;17:213–17.
27 Field TM. Stimulation of preterm infants. *Pediatr Rev* 2003;24:4–11.
28 Modrcin-Talbott MA, Harrison LL, Groer MW, *et al*. The biobehavioral effects of gentle human touch on preterm infants. *Nurs Sci Q* 2003;16:60–7.
29 Fabrizi L, Slater R, Worley A, *et al*. A shift in sensory processing that enables the developing human brain to discriminate touch from pain. *Curr Biol* 2011;21:1552–8.