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Functional Neuroimaging of Breastfeeding Analgesia by Multichannel Near-Infrared Spectroscopy

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Key Words

Cortical activation · Multisensory experience · Near-infrared spectroscopy · Pain in newborns

Abstract

Background: Newborns perceive pain, and several non-pharmacologic analgesic methods have been used during painful procedures. Activation of the neonatal somatosensory cortex, in association with a painful procedure without analgesia, has been demonstrated by two-channel near-infrared spectroscopy (NIRS). **Objectives:** To evaluate both cortical and behavioural responses of healthy term newborns to a painful procedure during two non-pharmacologic analgesic interventions, i.e. glucose solution and breastfeeding. **Methods:** The effects of glucose and breastfeeding on pain-associated neonatal cortical activity were studied in two groups (n = 30) by multichannel NIRS during a heel prick. Cortical activation was identified by variations in oxygenated haemoglobin. Neonatal pain expression was assessed by a validated scale. **Results:** No significant variations in cortical activity emerged using glucose solution, whereas breastfed newborns showed widespread cortical activation. Breastfed neonates showed significantly less behavioural pain expression. **Conclusions:** Glucose is associated with no significant

cortical activation and may interfere with pain-associated response at the cortical level. Conversely, breastfeeding analgesia is associated with generalized cortical activation and may act by multisensory stimulation, possibly overwhelming pain perception.

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Introduction

In the last decades, perception of pain in term and pre-term newborns has been demonstrated, and the need for analgesia has been widely accepted [1]. The oral administration of a sweet solution is the most commonly used non-pharmacologic analgesia in newborns, and both sucrose and glucose solutions are effective [2]. Breastfeeding may be an even more effective analgesic than sucrose during minor painful procedures [3].

Activation of the neonatal somatosensory cortex, in association with a painful blood sampling procedure without analgesia, has been documented by two-channel near-infrared spectroscopy (NIRS) at as early as the 25th week of gestation [4, 5]. The nociceptive-evoked activity in the brain has been proposed as an alternative and more direct measure of pain in infants [6]. Slater et al. [5] proposed to

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consider NIRS as a sensitive technique to study how analgesic strategies work at the cortical level, although a two-channel device can provide limited spatial resolution.

The aim of the study was to assess both cortical and behavioural responses of healthy term newborns to a painful procedure during two non-pharmacologic analgesic interventions, i.e. glucose solution and breastfeeding. Cortical activity was studied by multichannel NIRS, which provides better spatial resolution than a two-channel device. We tested the hypothesis that, during a painful procedure, a newborn's cortical activation would differ depending on the analgesic method used, and that breastfeeding would be a more effective analgesia than sweet solutions.

Methods

Patients

We enrolled 30 healthy full-term newborns (gestational age range: 38–41 weeks; 16 males and 14 females). They were on their third day of life when a heel prick for blood sampling was performed for metabolic disease screening. None of the newborns had previously experienced any painful procedure. Fifteen (8 males; 7 females) were given an oral glucose solution before the heel prick and 15 were breastfed during the heel prick. The assignment to a specific non-pharmacologic intervention was randomized. After a complete description of the study, written informed consent was obtained from the parents and the local committee for bioethics approved the research.

NIRS Recording

We used a multichannel NIRS device, the Hitachi ETG-100 (Hitachi, Tokyo, Japan), that records cortical haemoglobin variations from 24 channels by 18 optical fibres (optodes) of 1 mm in diameter placed on the scalp (10 light emitters and 8 light detectors). The optodes, arranged in two 3×3 patterns, were positioned on the left and right side of the head, providing 12 channels per hemisphere (fig. 1a, 2a). The distance between adjacent emitters and detectors was set at 2.5 cm. Cortical activation in the parietal, temporal and posterior frontal cortices of each hemisphere was studied.

Procedure

In the glucose group, the neonate was first placed on his/her back on a baby changing-table and the fibres were positioned on the infant scalp. A waiting period was allowed for the infant to get used to the equipment. Two minutes before starting the blood sampling procedure, a bolus of 2 ml of 20% oral glucose solution was administered.

In the breastfeeding group, the neonate was tested in his/her mother's lap. After placing optical fibres on the infant's scalp and waiting for the newborn to get used to the equipment, breastfeeding was started 2 min before the blood sampling procedure. Mothers were required not to talk to their newborns. Breastfeeding lasted until the blood sampling procedure was completed.

The NIRS signal was collected during the heel-prick procedure, as shown in figures 1b and 2b. The expression of pain during the

heel prick was assessed with the Neonatal Infant Pain Scale (NIPS) [7], which considers facial expression, crying, breathing pattern, arm and leg activity, and state of arousal. Assessments were performed by an investigator blinded to NIRS detection.

Data Analysis

Our analysis focused on the increase of cortical oxy-haemoglobin (HbO_2) during the heel-prick procedure as an estimate of cortical activation [8]. Possible components of the HbO_2 signal related to physiological noise or movements were removed by filtering the NIR signal.

The channels activated during the heel prick were identified by means of one-paired Student's *t* tests, comparing the baseline (the mean variation of HbO_2 in the 10 s before disinfection) to the pain-associated cortical response (the mean variation of HbO_2 in the 25 s following the actual heel prick). These analyses were processed, separately, in the group of newborns given glucose and in the group of breastfed newborns. In order to control for type I errors in multiple testing situations, we used a false discovery rate (FDR) approach, selecting a *q* value of 0.05 [9]. Possible differences in NIPS scores between the groups were compared by a non-parametric Mann-Whitney U test.

Results

In the glucose group, no channel survived the FDR threshold. Thus, no significant cortical activation was consistently observed during the heel prick in this group (fig. 1a). In the breastfed group, six channels survived the FDR threshold showing a HbO_2 increase during the heel prick, with three located on left hemisphere and three located on right hemisphere (fig. 2a): channel 1 ($t_{14} = -5.858$; $p = 0.0005$) on the left superior sensorimotor cortex, channels 6 ($t_{11} = -3.037$; $p = 0.0055$) and 9 ($t_{13} = -2.757$; $p = 0.008$) on the left somatosensory cortex, channel 14 ($t_{14} = -2.663$; $p = 0.0095$) on the right superior sensorimotor cortex, channel 17 ($t_{13} = -3.113$; $p = 0.008$) on the right posterior-superior frontal cortex, and channel 20 ($t_{11} = -3.228$; $p = 0.008$) on the right posterior parietal cortex. According to NIPS scores, the breastfed group (median = 3.0; interquartile range: 1.0–5.0) showed less intense pain behaviour than the glucose group (median = 5.0; interquartile range: 3.5–7.0; $Z = 2.092$; $p = 0.036$).

Discussion

In healthy full-term newborns experiencing a heel prick for blood sampling, we observed that following glucose administration there was no significant cortical activation consistently associated with the procedure. On the contrary, breastfed infants showed considerable cortical

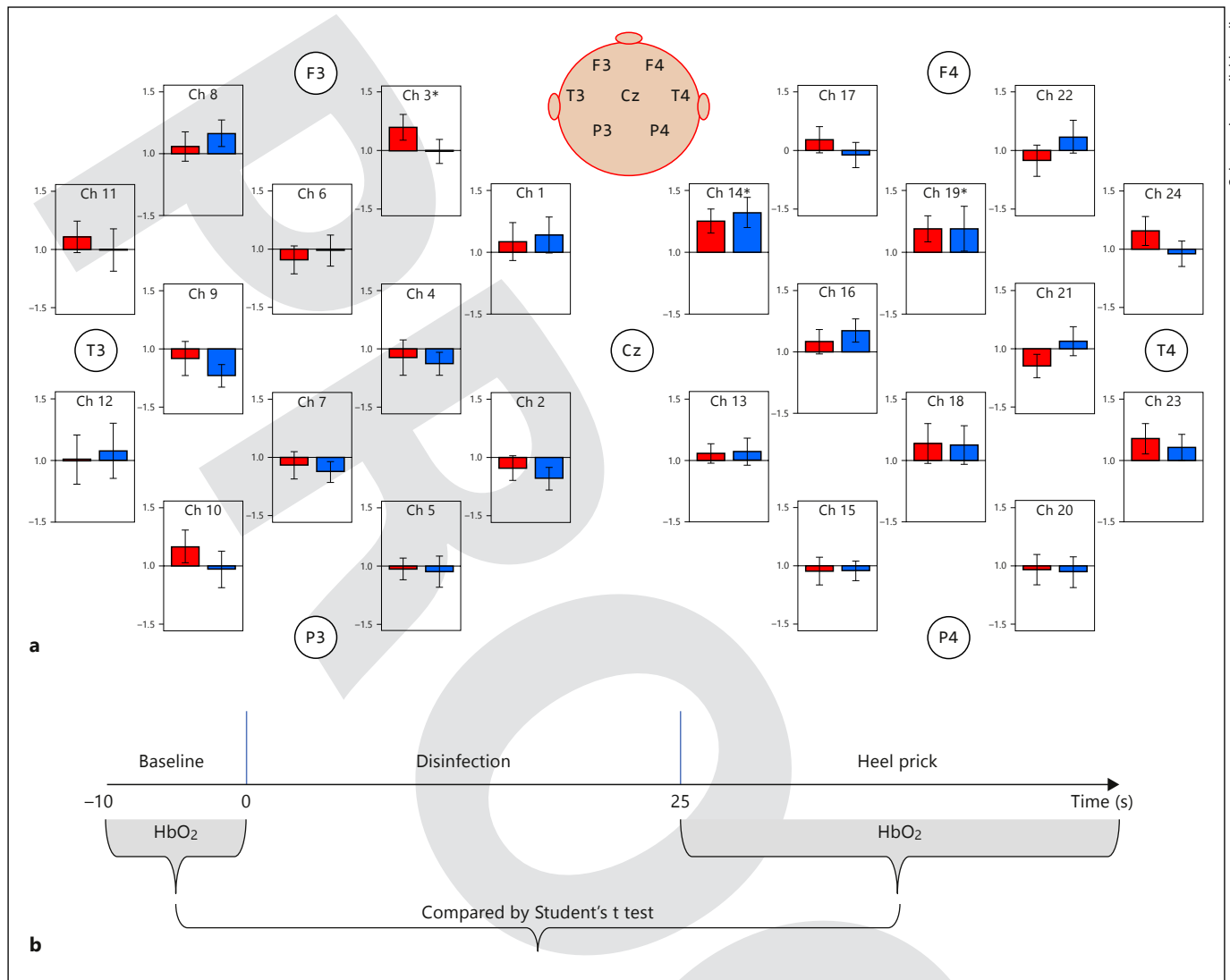


Fig. 1. a HbO₂ (red bar) and deoxy-haemoglobin (blue bar) mean variation in the 25 s following the heel prick observed in all 24 channels in the glucose group (n = 15). Their location is mapped in relation to the international 10-20 EEG system reference points (also reported on a schematic representation of the newborn's

head). * $p < 0.05$, but not passing the FDR threshold. Mean haemoglobin variation (\pm standard error), reported in mm/mm of the optical path length, is on the y-axis (± 0.5 mm/mm). **b** Timeline of the experimental procedure to detect baseline and pain-associated cortical activity during the heel-prick procedure.

activation in spite of lower NIPS scores than glucose-fed infants.

In agreement with our results, using pain behaviour evaluation, Codipietro et al. [3] showed that pain scores were lower with breastfeeding than with sweet solutions (sucrose). Conversely, using EEG, Slater et al. [6] found that nociceptive-evoked brain activity did not differ in newborn infants after administration of either sucrose or placebo in spite of lower behavioural pain scores in sucrose-fed infants. However, there are several differences

between Slater's study and our own study: (1) we used NIRS, which detects physiological activation exclusively from the cortex, while EEG may be influenced also by subcortical activity; (2) we analysed the vascular response in the 25 s following the painful stimulation, while Slater and colleagues considered the electrical signal detected in the first second after the stimulus, and (3) the cortical areas monitored were different between the two studies, as Slater's group considered only electrical activity detected at Cz according to the 10-20 EEG reference system, while

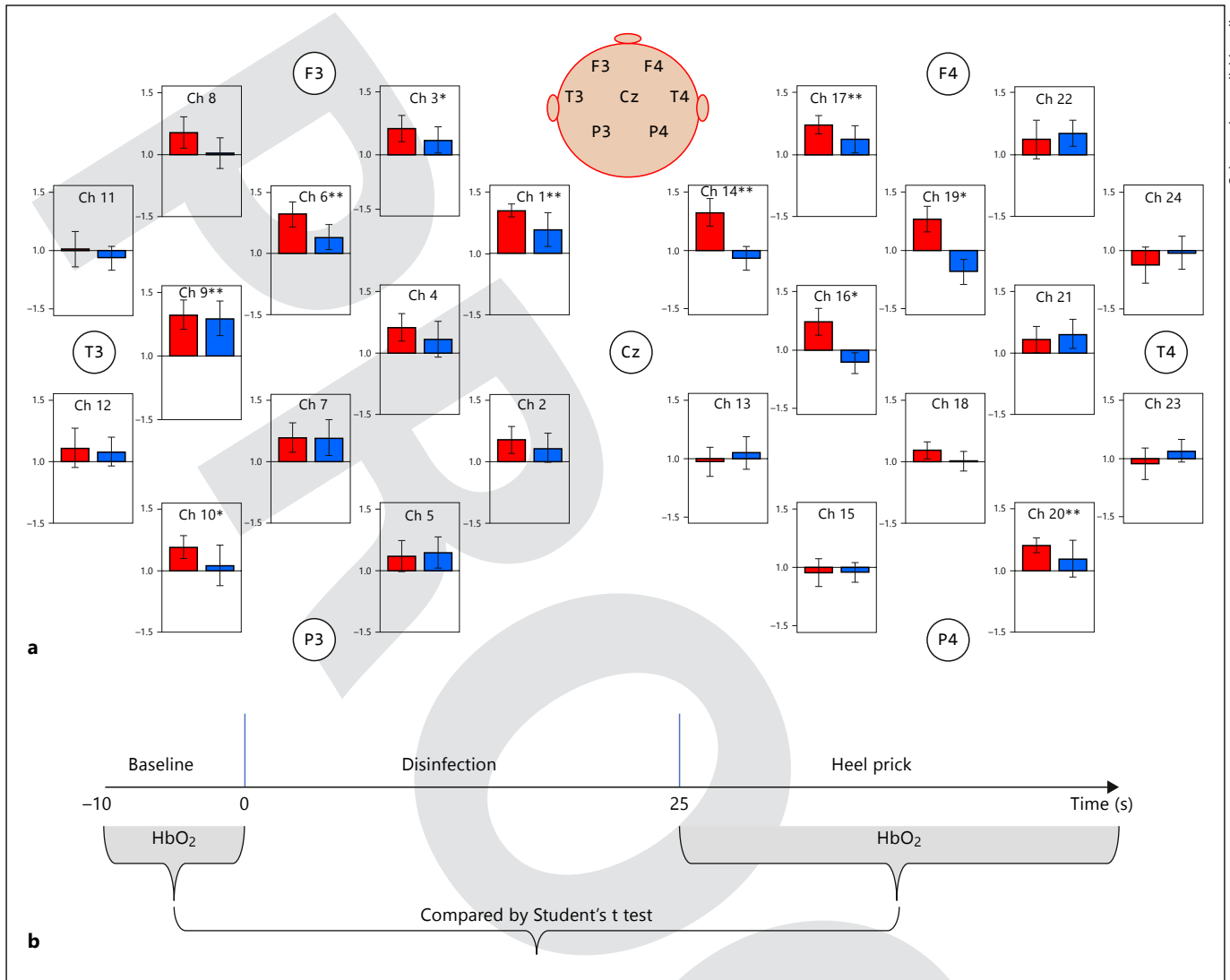


Fig. 2. a HbO₂ (red bar) and deoxy-haemoglobin (blue bar) mean variation in the 25 s following the heel prick observed in all 24 channels in the breastfed group ($n = 15$). Their location is mapped in relation to the international 10-20 EEG system reference points (also reported on a schematic representation of the newborn's

head). ** $p < \text{FDR } 0.05$; * $p < 0.05$, but not passing the FDR threshold. Mean haemoglobin variation (\pm standard error), reported in mm/mm of the optical path length, is on the y-axis (± 0.5 mm/mm). **b** Timeline of the experimental procedure to detect baseline and pain-associated cortical activity during the heel-prick procedure.

our region of interest was different and wider. Thus, our results appear to suggest that glucose may interfere with cortical-mediated pain behaviour, but we cannot exclude a pain-associated subcortical activation.

In addition to previous reports [e.g. 3], we demonstrated that breastfeeding is associated with diffuse cortical activation. Such a result may support the hypothesis that breastfeeding analgesia is mediated by a multisensory process [3]. We speculate that the stronger analgesic effect of breastfeeding might be attributed to a wider activation of the ce-

rebral cortex. Multiple simultaneous stimulations may interfere with pain perception [10]. In particular, we observed an important activation of the somatosensory region, which mediates the tactile, proprioceptive and thermal senses (besides pain). Olfactory and gustatory sensations might have also had a role in breastfeeding analgesia, but we did not monitor their cortical basis in our study. Moreover, we speculate that the activation of the posterior portion of the frontal cortex (channel 17) may imply an involvement of the motor cortex, e.g. due to sucking activity.

Our study has some obvious limitations. Infants were studied in different settings (changing table vs. mother's lap) that may independently influence the results. However, the settings we chose are those actually used in everyday clinical practice in every hospital. More research is clearly needed to assess the differential cortical responses to the different components of breastfeeding, such as body contention, sucking or breast milk itself. Additional limitations of our study are the small sample size and the lack of information on subcortical cerebral activation.

In conclusion, this pilot study confirms that breastfeeding is a very effective analgesic method in newborns and shows that it is associated with widespread cortical activation. We speculate that such cortical activation might be associated with a complex multisensory experience, possibly overwhelming pain perception.

Acknowledgements

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