Received: 24 May 2021 | Revised: 7 January 2022 | Accepted: 2 March 2022

DOI: 10.1111/ejn.15641

RESEARCH REPORT

EJN European Journal of Neuroscience FENS WILEY

Empathy at birth: Mother's cortex synchronizes with that of her newborn in pain

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Edited by: Susan Rossell

Abstract

Early neonatal relation with the caregiver is vital for newborn survival and for the promotion of an appropriate neural development. The aim of this study was to assess if the empathic cortical response of a mother to her baby's pain is synchronized with the neonatal cortical response to the painful stimulation. We used hyperscanning, a functional neuroimaging approach that allows studying functional synchronization between two brains. Sixteen mother–newborn dyads were recruited. Maternal and neonatal cortical activities were simultaneously monitored, by near-infrared spectroscopy, during a heel prick performed on the baby and observed by the mother. Multiple paired *t* test was used to identify cortical activation, and wavelet transform coherence method was used to explore possible synchronization between the maternal and neonatal cortical areas. Activations were observed in mother's parietal cortex, bilaterally, and in newborn's superior motor/somatosensory cortex. The main functional synchronization analysis showed that mother's left parietal cortex activity cross-correlated with that of her newborn's superior motor/somatosensory cortex. Such synchronization dynamically changed throughout assessment, becoming positively cross-correlated only after the leading role in synchronizing cortical activities was taken up by the newborn. Thus, maternal empathic cortical response to baby pain was guided by and synchronized to the newborn's cortical response to pain. We conclude that, in case of potential danger for the infant, brain areas involved in mother–newborn relationship appear to be already co-regulated at birth.

KEYWORDS
hyperscanning, interpersonal brain synchronization, mother–infant relationship, near-infrared spectroscopy, pain empathy

Abbreviations: COI, cone of influence; FDR, false discovery ate; HbO_2, oxyhaemoglobin; IBS, interpersonal brain synchronization; NIRS, near-infrared spectroscopy; OT, optical topography; ToM, theory of mind; WTC, wavelet transform coherence.

1 | INTRODUCTION

Early neonatal relation with the caregiver is indispensable for survival, and appropriate neural organization and psychophysical development of the child are promoted by such experience (Parsons et al., 2010). A good parental skill is mainly based on recognizing and meeting baby's needs (Swain, 2008). Effective relational abilities imply both empathy, a process of emotion sharing with the awareness that the origin of such emotion is the other person, and theory of mind (ToM), a process allowing to take another person's perspective by inferring and reasoning about his/her beliefs, thoughts and emotions (Preckel et al., 2018). Cognitive and affective neural underpinnings of such processes were explored in different studies.

Empathy has been associated with activation of inferior frontal gyrus, inferior parietal lobule (Gallese, 2007; Rizzolatti et al., 2009; Shamay-Tsoory, 2011), anterior and posterior cingulate cortex, medial prefrontal cortex and amygdala (Völlm et al., 2006). Empathy for other's pain, particularly, showed to be associated with the activation of anterior insula, anterior cingulate cortex, cerebellum (Decety & Jackson, 2006; Singer et al., 2004), somatosensory cortex (Avenanti et al., 2005) and superior temporal cortex (Decety, 2010; Timmers et al., 2018). In most of these areas, mirror neuron system networks were found (Gallese et al., 1996). Thus, empathy for other's emotional states, such as pain, activates a similar cortical activation in the observer and may be based on a 'mirror-matching' simulation of someone else's state (Gallese et al., 1996).

ToM, on the other hand, was associated with functional activation of medial prefrontal cortex, posterior superior temporal sulcus, temporal poles (Frith & Frith, 2003), ventral temporoparietal junction (Kanske et al., 2015), lateral orbitofrontal cortex, middle frontal gyrus, cuneus and superior temporal gyrus (Laillier et al., 2019; Völlm et al., 2006). Cerebral neuroimaging showed that empathy and ToM are associated with partially overlaid neural networks, such as the medial prefrontal cortex, the temporoparietal junction and the temporal poles (Kanske et al., 2015).

Most regions underlying both empathy and ToM processes appear to be involved in mother's cerebral response to emotional reactions from her own baby (Elmadih et al., 2016; Leibenluft et al., 2004; Lorberbaum et al., 1999; Noriuchi et al., 2008; Strathearn et al., 2005). Such regions are part of the 'parent brain' and mediate parent's reaction to the baby's needs (Kim et al., 2016; Swain, 2008). The parent brain consists of three interacting modules (reflexive, cognitive and emotional), which process parental feelings and behaviours, and aims to provide an effective parenting and to grant offspring survival (Swain, 2008). In this regard, we showed, by near-infrared spectroscopy (NIRS), that maternal left somatosensory and right superior temporal cortex respond to own baby pain, already a few days after birth (Bembich, Vecchiet, et al., 2016).

To study the possible functional synchronization between two or more brains engaged in a relationship, hyperscanning neuroimaging method has been proposed. Hyperscanning allows to study coherence in brain activities. Synchronization between brains (Pan et al., 2017) was initially studied in adults by fMRI (Montague et al., 2002) and, recently, by NIRS hyperscanning involving parent/child dyads (Reindl et al., 2018; Santamaria et al., 2020). During the interaction between a mother and her child, Reindl et al. (2018) demonstrated that the dyad's behaviour, emotions, subjective experience and neural activity were synchronized, either consciously or unconsciously.

The aim of this study was to assess if maternal empathic cortical response was synchronized with her infant's cortical response to a painful stimulation. We tested the hypothesis that the activated cortical areas of the mother, observing her baby pain, and those of the baby, experiencing the painful stimulation, would be functionally synchronized. Additionally, we hypothesized that the infant's cortical activity would lead the neural synchronization with the mother's cortical activity.

2 | MATERIALS AND METHODS

2.1 | Participants

We enrolled 16 mother–newborn dyads. Newborns (eight females, eight males) were full term, vaginally delivered, healthy, and on their second postnatal day. Their gestational age ranged between 38 and 41 weeks (mean: 39.4 ± 1), and their birth weight ranged between 2820 and 4060 g (mean: 3334 ± 392). Maternal age ranged from 18 to 41 years (mean: 32 ± 5.6), and educational level ranged from 8 to 18 years (mean: 12.2 ± 3.5). Seven mothers were primiparous, and nine were multiparous. Exclusion criteria were as follows: receipt of any medication, history of neurological or neurosensory disorder, psychosis, depressive or bipolar disorder, substance abuse or addiction. Moreover, post-partum depression symptoms were excluded by Edinburgh Postnatal Depression Scale assessment (Cox et al., 1987), as this condition can dampen mother's cortical reaction to her own baby pain (Bembich, Vecchiet, et al., 2016).

The study obtained the approval by the Institutional Committee for Bioethics (Prot. Nr.: RC 19/14). Written informed consent was obtained from both parents.

2.2 | Optical topography

Optical topography (OT) is a multichannel NIRS system allowing to monitor changes in cortical haemoglobin to detect and localize cortical activation. Optical fibers (or optodes), emitting and detecting near-infrared light, are used to detect regional cortical activation by measuring changes in the concentration of oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (Villringer & Chance, 1997). HbO_2 concentration increase is widely considered to reliably reflect cortical activation (Cui et al., 2012; Hoshi, 2007), basing on neurovascular coupling: Regional neuronal activation increases oxygen consumption, and, consequently, there is an increased blood flow and oxygenation as well. Each pair of adjacent emitter and detector fibers defines a single channel, which measures the light absorption by HbO_2 and deoxyhaemoglobin at the surface of the cerebral cortex (Villringer & Chance, 1997). OT, adopting a multichannel approach, has represented an improvement in spatial resolution, compared with one- or two-channel NIRS devices (Maki et al., 1995). Systems have been also developed to obtain an estimate of NIRS channel projections on a rendered adult (e.g. Ye et al., 2009) or infant brain (Kabdebon et al., 2014), although this is not available for newborns yet. NIRS allows a non-invasive, easy and portable functional monitoring of cortical activity for research purposes, and it has a very good feasibility when studies are conducted in the real-world setting (Yücel et al., 2021). However, detections are limited to the cerebral cortex, it has a lower spatial resolution than fMRI, and, due to the lack of accuracy and precision, it cannot be used alone for clinical purposes yet (Chen et al., 2020).

We used the Hitachi ETG-4000 OT device (Hitachi Medical Corporation, Tokyo, Japan), which can simultaneously record tracings from up to 48 channels. It emits near-infrared light at two wavelengths, 695 and 830 nm, and the reflected light is sampled once every 100 ms.

After analogue-to-digital conversion, values of changes in the concentration of HbO_2 in response to an experience are estimated as mM•mm units, that is, the product of the haemoglobin concentration changes, expressed in millimolar, and the optical path length, expressed in millimetres. The device is not invasive, well tolerated by participants, and is fairly resistant to movement artefacts.

In this study, 24 detecting channels were placed on mother scalp and 22 channels on newborn scalp, by rubber (mother) or silicone rubber (newborn) fibre holders, for a total of 46 detecting channels. On mothers, the optodes were arranged in two 3 × 3 patterns (18 optodes, 10 emitters and eight detectors) and positioned on the left and right side of the head, providing 12 channels on each hemisphere. On newborns, the optodes were arranged in a 3 × 5 pattern (15 optodes, eight emitters and seven detectors), positioned on the top of the head, but partially covering also the left and right side of the scalp, and providing 22 channels. The distance between adjacent emitters and detectors was set at 3 cm. Fibre holders were placed according to the international 10–20 EEG placement system (Jasper, 1958). In the mother, the central optode of the inferior channel row of each holder was placed over T3 on the left temporal region and over T4 on the right temporal region, maintaining the central channel column of holders in both cases on the virtual line joining T3 with C3 (central left) and T4 with C4 (central right). Thus, cortical activation was predominantly detected in the parietal, temporal and posterior frontal areas of each hemisphere (Figure 1a). In the newborn, the optode located in the middle of the fibre holder was placed over Cz, maintaining the central row of channels

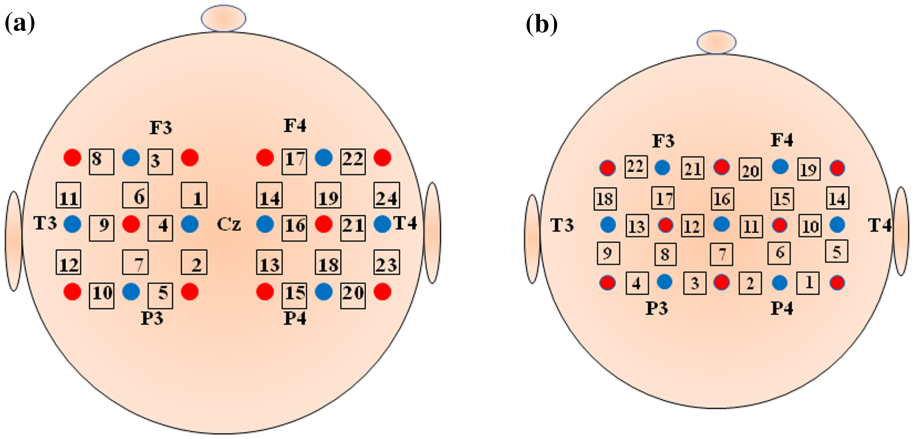

FIGURE 1 Representation, on a schematic head, of optical fibre location: (a) on left and right side of mother's scalp and (b) on newborn's scalp. (Red dots: near-infrared light emitters; blue dots: near-infrared light detectors; numbered squares: channels. The international 10–20 EEG system reference points are also reported)

on the bitragal reference curve and the central column of channels on the sagittal reference curve (Figure 1b). Thus, newborn's cortical activation was predominantly detected in the parietal and posterior frontal areas, bilaterally.

2.3 | Procedure

Dyad's cortical activation was tested on newborns' second day of life, during a heel-prick procedure for routine metabolic screening. During the experiment, any interfering visual and auditory stimulation was avoided. Each mother was seated in front of her newborn at a distance of 1.5 m, in a soft-lit and quiet room of the nursery ward of the maternity unit of the hospital. Newborns were laying on a changing table, in front of the mother. Two minutes before the heel prick, a 2-ml bolus of 20% oral glucose solution was given to all babies, as non-pharmacologic analgesia. Immediately after, optical fibres of the NIRS system were positioned on participants' heads, as described above, and the experimental procedure began. The experiment was divided into three phases: baseline, disinfection and painful stimulus.

The *baseline phase* lasted 20 s, during which the cortical hemodynamic response of the mother and her newborn was acquired without any stimulation of the baby.

In the 20 s during skin disinfection (*disinfection phase*), cortical hemodynamic response was acquired both in the mother, while seeing the nurse disinfecting her newborn's heel, and in the newborn, during the disinfection procedure.

The *painful stimulus phase* covered the first 20 s of the heel-prick procedure, during which mother's cortical response was recorded while she was seeing her newborn subjected to a painful stimulation and baby's cortical response was recorded during the execution of the heel prick and blood collection on a filter paper card. The precise moment in which disinfection and heel-prick procedure had to be performed was signalled to the nurse by the person collecting OT data, who manually marked such events precisely when they were performed, as already done in previous studies (e.g. Bembich, Marrazzo, et al., 2016). OT recordings from the dyad were acquired on the same computer; thus, events were marked at the same time on both mother's and baby's signal traces automatically.

2.4 | Data analysis

Our analyses focused on the variation of HbO_2 both of the mother during the observation and of the baby during the heel-prick procedure, compared with the baseline period. In a rat brain model, it was showed that changes in HbO_2 and in regional cerebral blood flow always show the same direction, whereas those in deoxyhaemoglobin are determined by changes in both venous blood oxygenation and volume. Furthermore, small changes in cerebral blood flow are not accompanied by any change in total haemoglobin concentration (Hoshi et al., 2001). Thus, HbO_2 signal showed to be more sensitive to changes in cerebral blood flow, during NIRS measurement, than other haemoglobins (Cui et al., 2012; Hoshi, 2007). In order to prevent motion artefacts, rapid changes in HbO_2 concentration (signal variations >0.1 mM•mm over two consecutive samples) were identified in the recorded data (Bembich et al., 2010) by the software already included in the OT device. We also visually checked the signals recorded in each channel of all participants, in order to detect low signal-to-noise ratio due to suboptimal transmission of near-infrared light (e.g. dark hair interference in the mother, movement in the baby). Data from channels with a signal interfered by motion artefacts or suboptimal transmission of near-infrared light, as specified above, were replaced, in the statistical analysis, with the mean of the entire data set (Yücel et al., 2021), as an esteem of central tendency, separately calculated for each experimental phase.

We identified cortical areas activated in the mother and in the baby during the procedure. Significantly activated channels were identified by Student's t tests corrected for multiple comparisons. For each mother's and baby's channel, we calculated the mean of relative HbO_2 changes during every experimental phase (baseline, disinfection and heel-prick procedure), each one lasting 20 s. To identify the activated channels, we performed one-tailed paired t tests in every channel, comparing HbO_2 mean changes: (1) between baseline and the hemodynamic response associated with disinfection and (2) between baseline and the hemodynamic response associated with heel prick. Analyses were performed separately for mothers and newborns. For those channels not respecting the statistical assumptions needed to perform a paired t test (e.g. a normal distribution of differences between pairs, verified by Shapiro–Wilk test), the significant activation was identified by non-parametric Wilcoxon test. A false discovery rate (FDR) approach was used to control Type I error in multiple testing situations ($q = 0.05$) (Singh & Dan, 2006). Statistical analyses of cortical activation were conducted using SPSS Version 22.0 for Windows (Armonk, NY, IBM Corp.).

We then explored the possible synchronization between the simultaneously activated cortical channels in mothers and babies (interpersonal brain synchronization [IBS]) during the procedure by wavelet transform

coherence (WTC) analysis (Cui et al., 2012; Grinsted et al., 2004). WTC is a method that can measure the cross-correlation between two time series, as a function of frequency and time (Torrence & Compo, 1998). WTC can find significant coherence even though the common signal power is low (Grinsted et al., 2004), as expected when the signal is collected simultaneously from an adult and a newborn brain. To estimate the statistical significance of the wavelet coherence, Monte Carlo simulation methods were applied by computing wavelet coherence for 300 randomly sampled surrogate data sets and comparing them to the actual data sets' coherence (see Grinsted et al., 2004 for further details). We used the wavelet coherence toolbox for Matlab by Grinsted et al. (2004), with contributions by Cui et al. (2012), provided on the following website: https://www.alivelearn.net/?p=1561. WTC analysis on two time series generates a 2-D coherence map, in which coherence intensity of the two-time series is evidenced on a graduated colour scale, from blue colour (low intensity) to yellow colour (high intensity). The statistical significance of cross-correlation ($P < 0.05$) is expressed, on the 2-D coherence map, by a thick contour surrounding frequency-synchronized signals over time. The direction of the relationship is expressed by arrows. Specifically, arrows pointing to the right indicate an in-phase relationship (e.g. signals move in the same direction), whereas arrows pointing to left indicate an anti-phase coherence (e.g. signals move in opposite directions). Furthermore, arrows pointing down, right down or left up all indicate that the first variable is leading the synchronization, whereas arrows pointing up, right up or left down all indicate that the second variable is leading the synchronization (e.g. if arrows point down, the first variable is leading the second variable by 90°; if arrows point up, the second variable is leading the first variable by 90°). In this study, each WTC analysis was performed including, as the first variable, the average time series of an activated channel in mothers and, as the second variable, the average time series of an activated channel in babies. Finally, because the wavelet is not completely localized in time, a cone of influence (COI) was introduced, where edge effects that might distort the analysis results and make them less reliable were shown as a lighter shade (see Figures 4–6).

3 | RESULTS

Using the Shapiro–Wilk test, non-normal distribution was found in some channels of both mothers and newborns. Specifically, during the *disinfection phase*, the difference between baseline and the haemodynamic response associated with disinfection was not normally distributed in Channels 3, 16, 17, 22 and 24 in mothers and in Channels 6, 9, 14, 16, 19 and 20 in newborns. During the *painful stimulus phase*, the difference between baseline and the haemodynamic response associated with heel prick was not normally distributed in Channels 12, 15, 17, 20, 22 and 24 in mothers and in Channels 4, 7, 8, 10, 14 and 15 in newborns. For all these channels, comparison with the baseline to identify a cortical activation associated with each specific stimulation was performed by non-parametric Wilcoxon test.

During the *disinfection phase*, no channel passed the FDR threshold ($P <$ FDR 0.05), either in the mother or in the baby. Thus, no significant cortical activation was detected when the heel was disinfected, neither in the observing mother nor in the infant subjected to the procedure.

During the *painful stimulus phase*, both the mother and the baby showed significant activations. Specifically, when the mother observed the actual heel prick performed on her baby, three channels passed the FDR threshold ($P <$ FDR 0.05): Channel 7 ($t_{15} = -4.540$; $P < 0.001$), located on left posterior parietal cortex; Channel 18 ($t_{15} = -3.117$; $P = 0.0035$), located on right posterior parietal cortex; and Channel 19 ($t_{15} = -3.000$; $P = 0.0045$), located on right anterior parietal cortex (Figure 2). When the baby was subjected to the heel-prick stimulation, the FDR threshold ($P <$ FDR 0.05) was passed by Channel 16 ($t_{15} = -3.589$; $P = 0.0015$), located on the most superior portion of the posterior frontal (motor) and parietal (somatosensory) cortex (Figure 3).

The IBS of activated cortical areas, during the *painful stimulus phase*, was assessed by WTC analysis. Three cross-correlations of averaged time series of mothers and babies were analysed: (1) between mother's left posterior parietal cortex (Channel 7) and the most superior portion of baby's motor/somatosensory cortex (Channel 16); (2) between mother's right posterior parietal cortex (Channel 18) and the most superior portion of baby's motor/somatosensory cortex (Channel 16); and (3) between mother's right anterior parietal cortex (Channel 19) and the most superior portion of baby's motor/somatosensory cortex (Channel 16).

By Monte Carlo estimation, WTC analysis including mother's left posterior parietal cortex (Channel 7) and the most superior portion of baby's motor/somatosensory cortex (Figure 4) revealed a main significant neural coherence of the dyads ($P < 0.05$) in the frequency band between 1.7 and 3.0 s (0.33–0.59 Hz), within a period of time between 4 and 12 s after the heel prick. Arrow direction and their inclination angle slightly and progressively changed throughout this time. Initially, we observed an anti-phase relationship led by the mother (arrows

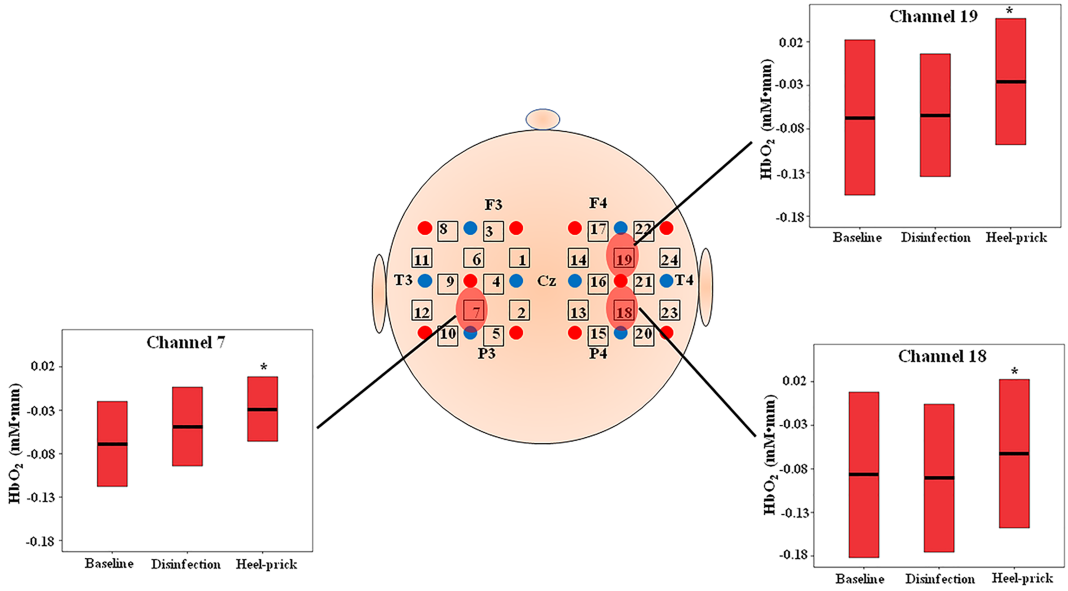

FIGURE 2 Oxyhaemoglobin (HbO_2) variation, reported on an error bar chart, during the three phases of the study (baseline, following disinfection and heel prick), in the three activated channels, when mothers were observing the painful stimulation performed on their own newborn (*P < FDR 0.05 compared to baseline). Channel's location is reported on a schematic head. Bars represent ±2 standard error variability around the mean (tick dash) of HbO_2 variation, which is reported on the y-axis in mM•mm unit (see text)

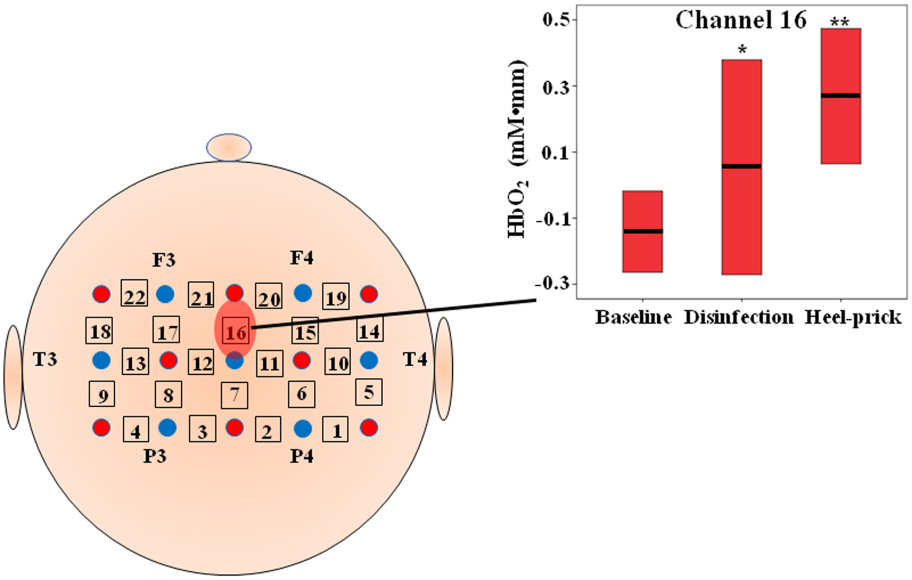

FIGURE 3 Oxyhaemoglobin (HbO_2) variation, reported on an error bar chart, during the three phases of the study (baseline, following disinfection and heel prick), observed in the activated channel, when newborns were subjected to the painful stimulation (**P < FDR 0.05 compared with baseline; *$P < 0.05$ compared with baseline, but not surviving P < FDR 0.05 threshold). Channel's location is reported on a schematic head. Bars represent ±2 standard error variability around the mean (tick dash) of HbO_2 variation, which is reported on the y-axis in mM•mm unit (see text)

pointing left up). Then, the relationship progressively lost the anti-phase synchronization, and the mother lost her leading role (arrows pointing progressively up).

Between the same areas, there were two other significant neural coherences ($P < 0.05$) in the frequency band between 0.4 and 0.8 s (1.25–2.5 Hz), within a period of time between 15 and 20 s after the heel prick. Arrow direction and inclination angle again slightly and progressively changed. In a first coherence period, between 15 and 17 s after the heel prick, we observed a leading role for the baby, with no clear in- or anti-phase direction of the relationship (arrows pointing up). In a second coherence period, between 18 and 20 s after heel prick, we observed an in-phase coherence led by the baby (arrows pointing right up).

There was also a fourth significant coherence period ($P < 0.05$) in the frequency band around 5.0 s (0.2 Hz), between 16 and 19 s after the heel prick, with arrows direction and angle inclination indicating an anti-phase relationship (arrows pointing to the left). However, this cross-correlation was totally outside the COI, thus not interpretable. Marginally, there were other sparse

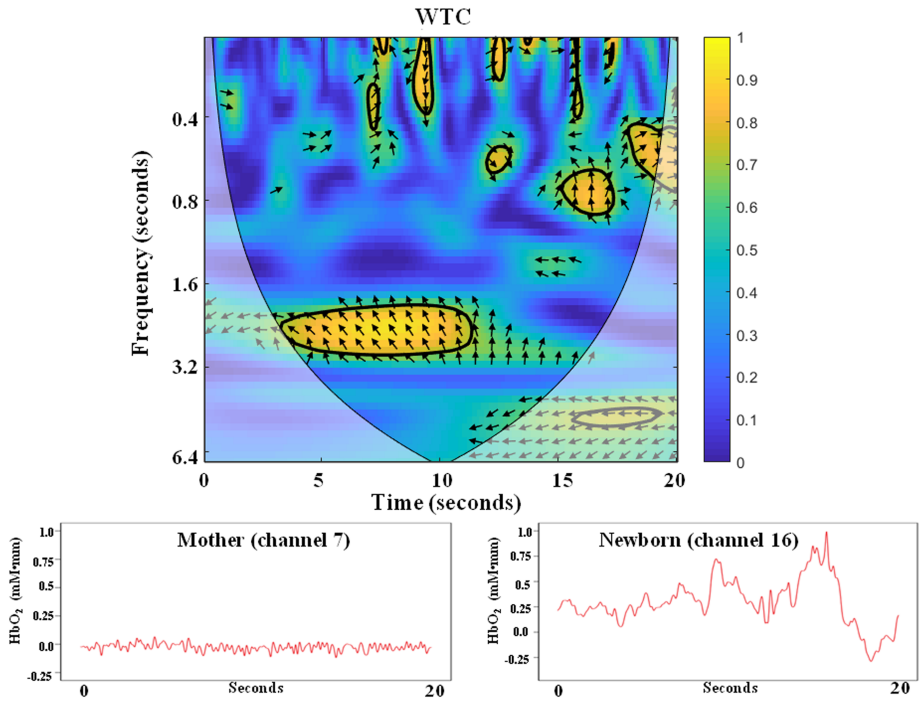

FIGURE 4 Interpersonal brain synchronization, explored by wavelet transform coherence (WTC), between average time series of raw oxyhaemoglobin (HbO_2) signal from mother's left posterior parietal cortex (Channel 7) and baby's superior motor/somatosensory cortex (Channel 16), collected during the 20 s following heel prick. WTC value is encoded on a colour scale, as indicated on the right bar, and the significance level against noise ($P < 0.05$), obtained by Monte Carlo methods, is showed as a ticked contour surrounding frequency synchronized signals. Variations in arrow direction and inclination angle of frequency synchronized signals indicate that the relationship between these dyad's activated cortical areas slightly and progressively changed throughout synchronization periods. The interpersonal brain synchronization falling outside the cone of influence (the area of the figure with a lighter shade) results are unreliable (see text for details). Time series of average HbO_2 variation collected during the 20 following heel prick from mother's left posterior parietal cortex (Channel 7) and baby's superior motor/somatosensory cortex (Channel 16) are also represented on the bottom. HbO_2 variation is reported on the y-axis in mM•mm unit (see text)

significant coherences in the band between 0.1 and 0.4 s (2.5–10 Hz), but all having a duration not exceeding 1 s.

WTC analysis on mother's right posterior parietal cortex (Channel 18) and the most superior portion of baby's motor/somatosensory cortex (Figure 5) revealed only one main significant neural coherence ($P < 0.05$) in the frequency band between 1.5 and 2.0 s (0.5–0.67 Hz), in a period of time included between 16 and 20 s after the heel prick. Arrow direction and their inclination angle generally indicated an anti-phase relationship led by the baby (most arrows pointing left down), but more than half of this cross-correlation was outside the COI and, therefore, not interpretable. Again, there were some other sparse significant coherences, in the band between 0.1 and 0.8 s, all lasting no more than 1 s.

WTC analysis including mother's right anterior parietal cortex (Channel 19) and the most superior portion of baby's motor/somatosensory cortex (Figure 6) revealed only some sparse significant coherences, in the band between 0.1 and 0.8 s (1.25–10 Hz), all lasting no more than 2 s.

4 | DISCUSSION

We studied the functional synchronization between the activated cortical areas of a mother, observing her infant's pain, and those of her infant, experiencing a painful stimulation (a heel prick for blood sampling). Our first finding was that the painful clinical procedure, performed on term infants, elicits a significant cortical activation both in the infant and in the mother observing the pain. Specifically, the infant shows an activation of the most superior portion of the primary motor/somatosensory cortex. Because the heel prick was painful, such cortical localization is compatible with a somatotopic representation of nociception processing in the newborn brain (Bembich et al., 2015; Goksan et al., 2015; Slater et al., 2010). In previous studies, we did not find a significant newborn's cortical activation, in association with heel prick, when an oral glucose solution was given as non-pharmacologic analgesia (Bembich et al., 2013, 2018). Such discrepancy may be explained by the fact that, in the present study, we monitored partially

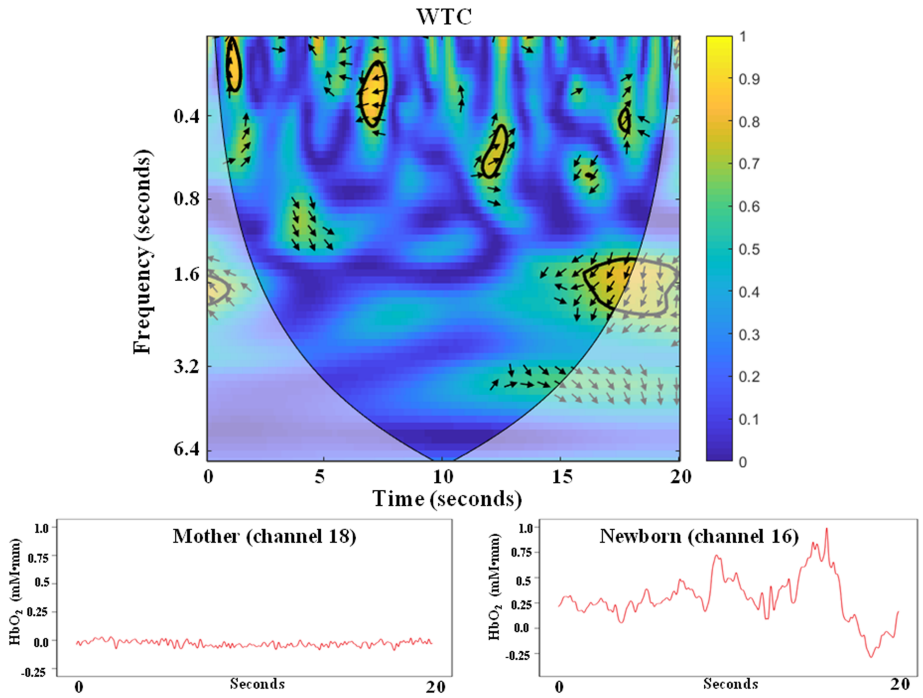

FIGURE 5 Interpersonal brain synchronization, explored by wavelet transform coherence (WTC), between average time series of raw oxyhaemoglobin (HbO_2) signal from mother's right posterior parietal cortex (Channel 18) and baby's superior motor/somatosensory cortex (Channel 16), collected during the 20 s following heel prick. WTC value is encoded on a colour scale, as indicated on the right bar, and the significance level against noise ($P < 0.05$), obtained by Monte Carlo methods, is showed as a ticked contour surrounding frequency synchronized signals. However, more than half of such interpersonal brain synchronization fell outside the cone of influence (the area of the figure with a lighter shade), thus resulting unreliable (see text for details). Time series of average HbO_2 variation collected during the 20 s following heel prick from mother's right posterior parietal cortex (Channel 18) and baby's superior motor/somatosensory cortex (Channel 16) are also represented on the bottom. HbO_2 variation is reported on the y-axis in mM•mm unit (see text)

different cortical areas and included the most superior portion of the primary motor/somatosensory cortex, not assessed in our earlier research. Using EEG, Slater et al. (2010) found that a similar region was activated when a painful procedure was performed in newborns, even if sucrose analgesia was given. NIRS is not the only technique that can reliably detect newborn cortical activation, as also EEG (e.g. Slater et al., 2010) and, less often, fMRI (e.g. Goksan et al., 2015) were effectively applied to this population. We used a multichannel NIRS system, because it has already proven suitable in cerebral hyperscanning involving children (Reindl et al., 2018). Additionally, we had successfully used it to detect newborn cortical activity in association with a nociceptive stimulation (e.g. Bembich et al., 2015).

When observing a heel prick done on her own newborn, the mother showed a bilateral activation of the posterior parietal cortex. Maternal cortical activation involved also the right anterior parietal cortex. The activation of these areas, which include the somatosensory cortex, was already observed in association with empathy in general (Gallese, 2007; Rizzolatti et al., 2009; Shamay-Tsoory, 2011) and empathy for pain in particular (Avenanti et al., 2005; Gu & Han, 2007; Lamm et al., 2007). The maternal parietal cortex has already been shown to respond specifically to own baby pain (Bembich, Vecchiet, et al., 2016). This area hosts mirror neuron system circuits (Gallese et al., 1996; Keysers & Gazzola, 2014), which are considered to mediate a 'mirror-matching' simulation process of someone else's emotional state. Such area is also considered part of the cognitive module in the parent brain, which has been proposed to regulate parent–infant interpersonal synchrony, to predict infant's needs and to plan subsequent parent's behaviour (Swain, 2008).

We previously reported that mother's left parietal cortical response to her own baby pain was negatively correlated with post-partum depression symptoms (Bembich, Vecchiet, et al., 2016). Thus, mother's left parietal cortex, both containing mirror neuron systems (Gallese et al., 1996; Keysers & Gazzola, 2014) and being part of the parent brain (Swain, 2008), may play a role in mediating the mother's response to her own infant's pain.

Planning parent behaviour is the function proposed for the cognitive module in the parent brain (Swain, 2008). We speculate that the parietal area may be

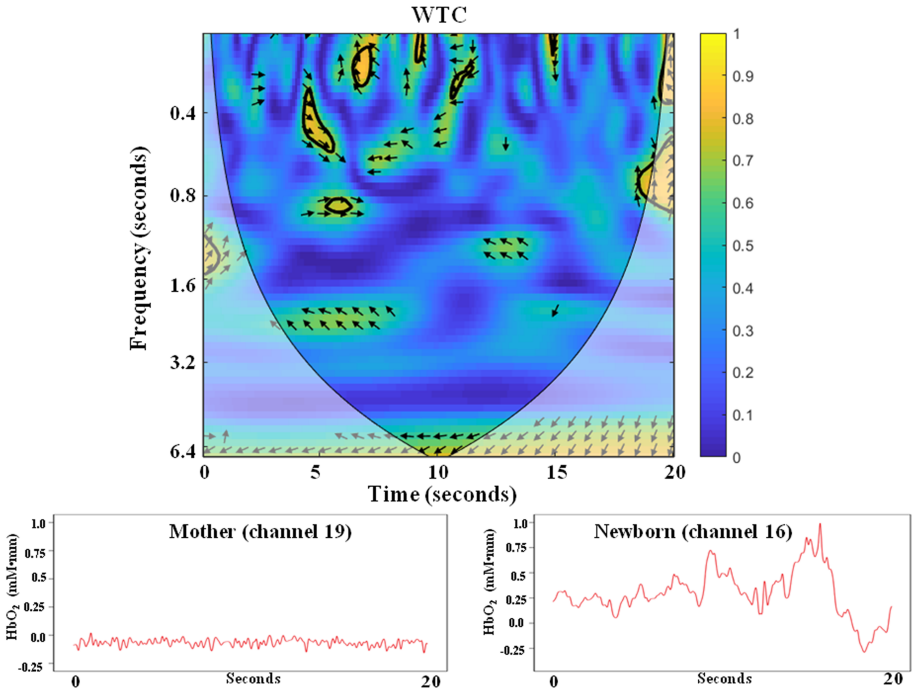

FIGURE 6 Interpersonal brain synchronization, explored by wavelet transform coherence (WTC), between average time series of raw oxyhaemoglobin (HbO_2) signal from mother's right anterior parietal cortex (Channel 19) and baby's superior motor/somatosensory cortex (Channel 16), collected during the 20 s following heel prick. WTC value is encoded on a colour scale, as indicated on the right bar, and the significance level against noise ($P < 0.05$), obtained by Monte Carlo methods, is showed as a ticked contour surrounding frequency synchronized signals. Some sparse significant coherences, in the band between 0.1 and 0.8 s (1.25–10 Hz) and all lasting no more than 2 a, could be observed. Time series of average HbO_2 variation collected during the 20 s following heel prick from mother's right anterior parietal cortex (Channel 19) and baby's superior motor/somatosensory cortex (Channel 16) are also represented on the bottom. HbO_2 variation is reported on the y-axis in mM•mm unit (see text)

involved in complex functions in parenting behaviour, like understanding newborn's needs and planning a response to ensure progeny survival when a threat is perceived.

Our second finding was the presence of a complex functional synchronization between maternal and neonatal brain. Such functional coherence was observed between mother's left posterior parietal cortex and the most superior portion of baby's motor/somatosensory cortex, lasting about 13 s out of a total of 20 monitored seconds, following the heel prick (from the 4th to the 12th second and from the 15th to the 20th second). Throughout this time, the phase and the leadership in the neural synchronization dynamically changed. An initial anti-phase synchronization led by the mother, which we speculate may be due to an anticipation of her own baby's cortical response to heel prick (the newborn was not aware to be observed by the mother, thus is not plausible that she could led his/her cortical activation, but rather that she could anticipate it), was progressively replaced by the newborn's lead. Then, between 15 and 20 s after the heel prick, and in faster frequency bands, IBS changed again, shifting to an in-phase synchronization between mother and newborn's cortical activation, still led by the baby.

To our knowledge, this is the first time that the functional synchronization between maternal and neonatal brain is studied shortly after birth, during an emotionally meaningful condition, such as baby pain. Functional synchronization between maternal and neonatal brain changed throughout the 20 s following the heel prick, becoming positively cross-correlated only after the leading role in synchronizing cortical activities had been taken up by the newborn. On the contrary, when the mother's cortical activity initially seemed to anticipate that of her newborn, subjected to a painful stimulation, a negative cross-correlation in the cortical synchronization was observed. Thus, the empathic cortical response of the mother, observing a potentially threatening procedure involving her newborn, appeared to be guided by the newborn's cortical response to such procedure.

Functional synchronization between human brains have been observed later in life, both in adults (Cui et al., 2012; Kinreich et al., 2017; Liu et al., 2017; Montague et al., 2002; Pan et al., 2017) and children (Miller et al., 2019; Reindl et al., 2018; Santamaria

et al., 2020). In the context of the primary relationship, we have shown that such synchronization is already present shortly after birth, at least when emotional involvement and potential threat to the infant are present.

Other functional coherence, between mother's left and right posterior parietal cortex and the most superior portion of baby's motor/somatosensory cortex, fell outside the COI, thus resulting unreliable to interpret. We found no IBS between mother's right anterior parietal cortex and baby's superior motor/somatosensory cortex. We previously found that the maternal right hemisphere may have a different functional role in responding to baby pain, when compared with the left hemisphere (Bembich, Vecchiet, et al., 2016). This seems to hold true also when IBS is studied.

We speculate that mother's left posterior parietal cortex may play a more important functional role than right parietal cortex in the processing of parental behaviour elicited by empathic responses to baby pain, at least in terms of timing and synchronicity. Of note, IBS between mother's left posterior parietal cortex and the most superior portion of newborn's motor/somatosensory cortex seemed to last beyond the 20 monitored seconds after heel prick.

Thus, the first limitation of this study is that the recording of the cortical activity was limited to the first 20 s after heel prick, but we cannot exclude the possibility that IBS could emerge or last beyond such time span. Second, NIRS technique is unable to detect brain activation below the cerebral cortex, whereas our procedure may elicit subcortical activations both in the mother (Swain, 2008) and in the newborn (Goksan et al., 2015). As an example, the so-called medial nociceptive pathway, which has been related to affective and motivational aspects of pain, includes both the anterior cingulate cortex regions and the intralaminar thalamic nuclei (Vogt & Sikes, 2000). Third, our study population was very small. It is possible that individual differences between mothers, in terms of personality or previous experience with own and others pain, could had impacted NIRS data. Thus, our results need to be confirmed in larger samples, possibly also collecting more information about the above mentioned maternal psychological aspects. Fourth, a further OT limitation is its lack of anatomical precision (Chen et al., 2020) due to the presence of a fixed interoptodic distance (e.g. 3 cm) in the fibre holder, which is placed on heads of different size and shape. As a possible solution to such OT limitation, the use of a device with increased optode density has been suggested (Chen et al., 2020). The co-registration of OT optode locations to an individual subject's anatomy, via previously acquired MRI, could be an alternative. We did not have the possibility to adopt either solution. However, we previously applied the same technique to study the cortical response of mothers watching their own baby pain. We found an activation of maternal left primary somatosensory cortex (Channel 4) and right superior temporal cortex (Channel 21) (Bembich, Vecchiet, et al., 2016). Therefore, in both our studies, performed on participants with heads of different size and shape, maternal cortex was activated in channels situated in close proximity to one another (see Figure 1a): Channels 4 and 21 in the previous study (Bembich, Vecchiet, et al., 2016) and Channels 7, 18 and 19 in this one. Fifth, a single trial in each participant may be not sufficient to obtain a good signal-to-noise ratio in the collected data, thus affecting the quality of our results, but this is entirely justified by obvious ethical reasons. Moreover, previous research using single trial NIRS data to study newborn cortical activation associated with a necessary clinical painful stimulation has been already published (e.g. Bartocci et al., 2006; Bembich et al., 2015; Slater et al., 2006).

To our knowledge, however, this is the first time that hyperscanning is applied to the attachment relationship with the primary caregiver, exploring IBS between a mother and her own baby shortly after birth. Moreover, the experimental procedure included a realistic potential threat to the baby's integrity.

To conclude, neurophysiological co-regulation processes, or IBS, between two brains, are present shortly after birth in the attachment relationship between mother and infant. This co-regulation may allow to adjust brain activities towards adaptive purposes, in relation to newborn's needs or to a negative event, like a painful stimulation. Based on the above, we speculate that the synchronized activation of specific areas of maternal and neonatal brains may represent a neural marker of mother's caring relationship towards her newborn (Panksepp, 1998). Further research is needed to assess (1) whether clinical conditions, such as post-partum depression, can alter mother/infant's brain co-regulation and (2) whether synchronicity is different during a reciprocal positive relationship, such as breastfeeding.

ACKNOWLEDGEMENT

Dr S. Bembich was supported by a grant from the Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", Trieste, Italy (N. 2/17).

CONFLICT OF INTEREST

The authors declare no conflict interest.

AUTHOR CONTRIBUTIONS

SB conceived and designed the study, acquired NIRS data, interpreted the results and drafted the manuscript.

AS and LT contributed to the interpretation of the results and revised the manuscript. SM acquired NIRS data and contributed to the drafting of the manuscript. GDR and GC contributed to the NIRS data acquisition and revised the manuscript. SD conceived and designed the study, interpreted the results and revised the manuscript. All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author has had full access to the data in the study and final responsibility for the decision to submit for publication.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15641.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Mendeley Data repository at https://data.mendeley.com/datasets/7fvhjnppdv/3.

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How to cite this article: Bembich, S., Saksida, A., Mastromarino, S., Travan, L., Di Risio, G., Cont, G., & Demarini, S. (2022). Empathy at birth: Mother's cortex synchronizes with that of her newborn in pain. *European Journal of Neuroscience*, *55*(6), 1519–1531. https://doi.org/10.1111/ejn.15641