PAPER

Neural time course of pain observation in infancy

Margaret Addabbo[1] | **Nadia Bolognini**[1,2] | **Chiara Turati**[1]

[1]Department of Psychology & Milan Center for Neuroscience (NeuroMi, University of Milan-Bicocca, Milan, Italy

[2]Laboratory of Neuropsychology, IRCCS Istituto Auxologico Italiano, Milan, Italy

Correspondence
Margaret Addabbo, Department of Psychology, University of Milan-Bicocca, Piazza Ateneo Nuovo, 1 (U6), 20126 Milan, Italy.
Email: margaret.addabbo@unimib.it

Abstract

Perception of pain in others is of great evolutionary significance for the development of human empathy. However, infants' sensitivity to others' painful experiences has not been investigated so far. Here, we explored the neural time course of infants' processing of others' pain by measuring event-related brain potentials (ERPs) while 6-month-old infants observed a painful tactile stimulation directed towards the eye and a neutral tactile stimulation on the eyebrow. We analyzed both the *Negative Central* (Nc) and the later *Late Positive Potential* (LPP) ERP components, indexing respectively attention allocation and cognitive evaluation of perceptual stimuli. Results showed that observing painful touch elicits a mid-latency Nc (300–500 ms) over the right fronto-central site, which is greater in amplitude as compared to neutral touch. A divergent activity was also visible in the centro-parietal early (550–750 ms) and late (800–1000 ms) LPP, showing increased amplitudes in response to neutral compared to painful touch. The cognitive evaluation of painful stimuli, reflected by the LPP, might thus not be fully developed at 6 months of age, as adults typically show a larger LPP in response to painful as compared to neutral stimuli. Overall, infants show early attentional attuning to others' pain. This early sensitivity to others' painful tactile experiences might form a prerequisite for the development of human empathy.

KEYWORDS
body knowledge, empathy, event-related brain potentials, infancy, pain observation, touch

1 | INTRODUCTION

When we observe somebody in a painful situation, we share his/her affective states and show empathic concern (Decety & Meyer, 2008). A great amount of evidence shows that human infants can share others' affective states through a process named emotional contagion or affective resonance/arousal and react to negative and positive emotional cues derived from the other (Addabbo et al., 2020; Kaiser et al., 2017). For example, recent electromyographic studies have shown that infants respond to emotionally congruent facial expressions to happy and fearful faces by 7 months of age (Kaiser et al., 2017) and to happy and angry action kinematics at 11 months (Addabbo, Vacaru, et al., 2020). In addition, newborn infants respond to others' cry by showing negative emotions and distress (Dondi et al., 1999). Also, some early signs of empathic concern

for others have been found during the first year of life: by 8 months of age, infants are attuned to their mothers' and peers' distress by showing expressions reflecting concern and early attempts to comprehend others' emotional state (Liddle et al., 2015; Roth-Hanania et al., 2011).

Interestingly, infants can resonate not only with others' emotions but also with others' sensory experiences. Direct evidence comes from electrophysiological studies showing the engagement of infants' somatosensory system during the visual observation of someone else being touched (Addabbo et al., 2020; Meltzoff et al., 2018; Rigato et al., 2019). For example, 4-month-olds somatosensory event-related brain potentials (ERPs) to a vibrotactile stimulation on their hand are modulated by the simultaneous observation of a touch (Rigato et al., 2019). Furthermore, somatosensory areas are somatotopically activated both when 6-month-olds observe a tactile stimulation on others' body parts (hand and foot) and when

they feel a tactile stimulation on their own body parts (Meltzoff et al., 2018). Thus, infants detect the equivalence between a tactile sensation on others' body and the sensory consequence that such tactile experience has on their own body. This has been taken as evidence of the early involvement of a shared neural circuitry that allows infants to match their own sensory experiences to others' experiences (Addabbo, Quadrelli, et al., 2020; Meltzoff et al., 2018; Rigato et al., 2019) as shown in adults (e.g., Bolognini et al., 2011; Keysers, 2010). Overall, converging findings show that in the first year of life, infants detect and share others' affective states and sensory experiences and show the very first signs of empathic concern for others' distress. These primary emotional responses will refine during development leading to the emergence of more advanced empathic processes, such as emotion regulation, perspective-taking abilities, and prosocial behaviors (Decety, 2015).

Notwithstanding the relevance of the literature reviewed above, so far, little is known about infants' sensitivity to the observation of painful tactile stimulations. Pain observation paradigms have been extensively used to study the neural basis of empathy by using very simple stimuli depicting limbs (Fan & Han, 2008) or faces (Contreras-Huerta et al., 2013; Sessa et al., 2014) in painful situations. Indeed, the perception of pain in others is considered of great evolutionary significance for the development of morality and prosocial behaviors, such as helping, sharing, and comforting (Decety & Cowell, 2018). In adults, it has been demonstrated that observing body parts in painful and neutral situations activates areas involved in both affective and sensory processing, which are also activated during first-person experiences of pain (Singer et al., 2004). Also, pain processing follows a two-stage temporal dynamics, as shown by several ERPs studies (Fan & Han, 2008; see also Coll, 2018, for a meta-analysis). In particular, painful stimuli elicit an early, automatic N2 component that reflects emotional sharing, and later ERP components, such as the P3 and the Late Positive Potential (LPP), indexing cognitive evaluation of others' pain (Coll, 2018; Fan & Han, 2008). Similar early and late components were also found in children during passive observation of physical injuries to others (Cheng et al., 2014; Decety et al., 2018). Age-related changes were found in the amplitude of the early N2 and LPP between 4.5 and 9 years of age: the N2 decreases and the LPP increases in amplitude throughout development, indicating an evolution in children's reactions from personal affective sharing to other-oriented behaviors, such as helping, sharing, and comforting (Cheng et al., 2014).

So far, infants' neural processing in response to the observation of others' pain remains unknown. Studies that explored empathy for pain in adults and children typically used stimuli depicting body parts in painful everyday situations. However, infants have little or no experience in observing injuries produced by objects (e.g., scissors, needles) on the human body. Rather, infants might have accumulated some knowledge about the types of self-produced actions that could be harmful or not and the delicacy of some of their body parts. Notably, infants start to discover their bodies already inside the womb via self-generated touch (Piontelli, 1987). During prenatal life, fetuses change the kinematics of their hand movement

according to the body part that is going to be touched. Specifically, fetuses' hand movements are decelerated when the target is a delicate and sensitive body part as the eye compared to the mouth (Zoia et al., 2007). After birth, infants extensively explore their body and face (Thomas et al., 2015), and these spontaneous day-to-day tactile activities might provide them with redundant information about the area of the body being touched. Thus, infants do have some knowledge about the sensitivity/delicacy of their own body parts and the sensory consequences of touch on their faces.

Here, we explored infants' neural processing of others' pain. We measured ERPs while 6-month-olds observed a painful tactile stimulation directed toward the eye and a neutral tactile stimulation toward the eyebrow. Consistent with previous electrophysiological studies investigating pain processing in older children and adults (Cheng et al., 2014; Decety et al., 2018; Fan & Han, 2008), we analyzed both attentional and later cognitive ERP responses to observed painful and neutral tactile experiences. We expected greater amplitudes in response to pain over the fronto-central Negative central (Nc), indicating a prompt reaction to others' pain, possibly due to emotional sharing and attention allocation to salient, emotional stimuli. Indeed, the Nc is a typical infant-ERP component, reflecting the allocation of attentional resources toward salient stimuli in infancy (Reynolds & Richards, 2005; Richards, 2001). For example, previous literature has shown enhanced activity of the Nc in response to angry faces compared to fearful or happy expressions across the first year of life (Xie et al., 2019) and to prosocial compared to antisocial scenes at 12 months of age (Cowell & Decety, 2015). Together with the relatively automatic mid-latency Nc, we have also explored differential activity over the following, cognitive, LPP over centro-parietal electrode sites in an early (550–750 ms) and late (800–1000 ms) time window (Cheng et al., 2014; Decety et al., 2018). Studies with children highlighted a developmental trajectory of the LPP. Such component shows increased responses to neutral scenes compared to painful stimuli in very young children (3.5–5 years of age; Decety et al., 2018), overall increased amplitudes across childhood (Cheng et al., 2014), and a mature pattern of responses with larger LPP in response to painful stimuli in older children (4.5- to 9-year-olds; Cheng et al., 2014) and adults (Coll, 2018). Such LPP changes are considered reflecting the progressive development of top-down regulatory abilities, which are essential to

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Research Highlights

- Six-month-old infants show neural differentiation between painful and neutral tactile stimulations to others both over the attentional Nc and the later, cognitive, LPP ERP component.
- Infants exhibit enhanced Nc in response to pain and enhanced LPP in response to neutral touch.
- Six-month-old infants show to be sensitive to others' painful tactile experiences.

down-regulate the processing of painful images (Cheng et al., 2014). The visual LPP (also named late positive component, Pc, in the infant literature) was also explored in infancy and varied as a function of emotions (Grossmann et al., 2006; Missana et al., 2015; Nelson & de Haan, 1996). Thus, giving the evolution of the LPP across ages, it is plausible to hypothesize to find an immature pattern of response over the LPP in 6-month-olds, with enhanced activity in response to neutral over painful stimuli over centro-parietal sites.

2 | METHODS

2.1 | Participants

The final sample included 20 healthy full-term 6-month-olds (11 female infants, mean age = 180.6 days, range = 164–198 days). An additional 25 infants were also tested but were not included in the final sample due to fussiness (e.g., crying or manifesting discomfort by moving restlessly, resulting in early termination of the testing session; N = 6) and no completion of an adequate number of trials to be considered for data analysis (8 trials per condition; N = 10; e.g., infants who were still and attentive but for a short period) or eye and body movements that resulted in excessive recording artifacts (e.g., infants who moved a lot but were attentive; N = 9). This high dropout rate is typical in EEG studies with infants (Stets et al., 2012). An a priori power analysis indicated that 19 participants would be needed in order to have 85% probability of detecting a significant effect ($\alpha = 0.05$) with a medium effect size ($r = 0.25$; Cohen, 1992) using our experimental design in the repeated measures ANOVA.

Parents were informed about the procedure and gave their written consent to their child's participation. The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and approved by the Ethical Committee of the University of Milano-Bicocca (Protocol number 236). Parents gave their written informed consent.

2.2 | Stimuli, apparatus, and procedure

The experiment took place in an electrically shielded Faraday cage. Infants were seated on the parent's lap (who was asked to keep the eyes closed during the experiment) approximately 60 cm from a 24-inch on which stimuli were presented. A video camera above the screen recorded the infant for off-line coding of eye and body movements. Two stimuli were presented to the infant: (i) a hand moving and touching with the index finger the eye of an actress (pain condition); (ii) a hand moving and touching with the index finger the eyebrow of an actress (neutral condition). Each stimulus was composed of two frames. The first frame was the same in both stimuli and displayed a hand positioned in front of the profile of a female face. The second frame differed in the two experimental conditions: in the pain condition, the index finger touched the eyeball of the eye of the actress; in the neutral condition, the index finger touched the

eyebrow of the face (Figure 1a). Each frame lasted for 1000 ms, and the transition from frame 1 to frame 2 gave the impression of the movement of the index finger toward the two target locations of the face. The amount of movement was kept constant between the two stimuli by equalizing the distance of the hand in frame 1 to the final target (eyebrow or eye) in frame 2 (2° of visual angle). The dimension of the face at a distance of 60 cm from the screen was 14.7° of visual angle in height and 16.1° in width. The dimension of the hand was 4.3° of visual angle in height and 14.7° in width. The distance of the index finger from the face in the first frame was 1° of visual angle. Each trial started with a fixation cross of variable duration (1000–1200 ms) displayed in the center of the screen. Then, one of the two stimuli was presented to the infant. There was no restriction in the number of trials shown, that is, they could be played indefinitely until the infants lost interest in them or got fussed (i.e., until the infants did not watch the stimuli for five consecutive trials). The mean number of trials presented was 32.3 (min 21–max 49) for the pain condition and 32.3 (min 22–max 49) for the neutral condition. The two experimental conditions were presented in a pseudorandomized order by E-prime 2.0 software.

Stimuli were validated by 21 adults (16 females, mean age = 28.95 years, SD = 10.33), who were asked to judge on a 7-point Likert-scale: (i) how painful was the touch, from 'not painful at all' (−3) to 'very painful' (+3); (ii) How arousing was the touch, from 'not arousing' (−3) to 'very arousing' (+3); and (iii) the valence of the touch, from 'very negative' (−3) to 'very positive' (+3). Paired sample t-tests revealed that the touch in the eye was rated as more painful (mean = 1.62, SD = 1.28) compared to the neutral touch (mean = −1.90, SD = 1.44; $t(20) = 8.67$, $p < 0.001$), more arousing (mean = 0.67, SD = 1.68) than the neutral stimulus (mean = −1.95, SD = 1.59, $t(20) = 5.96$, $p < 0.001$), and more negative (mean = −1.57, SD = 1.03) than the neutral one (mean = 0.00, SD = 0.63, $t(20) = 6.42$, $p < 0.001$).

2.3 | ERP recording and analysis

Continuous scalp EEG was recorded from a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesic) that was connected to a NetAmps 300 amplifier (Electrical Geodesic) and referenced online to a single vertex electrode (Cz). Channel impedance was kept at or below 100 KΩ, and signals were sampled at 500 Hz. EEG data were pre-processed off-line using NetStation 4.5 (Electrical Geodesic). The EEG signal was segmented in 1000 ms epochs and was target locked to frame 2, when the crucial event occurred (touch on the eyebrow or aye), with a baseline period beginning 100 ms before the onsets. Data segments were filtered using a 0.3–30 Hz band-pass filter and baseline corrected using mean voltage during the 100 ms pre-stimulus period. We adopted a careful procedure to eliminate movement artifacts. Firstly, all trials containing more than 15% of channels with signals exceeding ±200 mV were detected and excluded via an automated algorithm. Data were then inspected manually to discard channels containing eye movement, body movements,
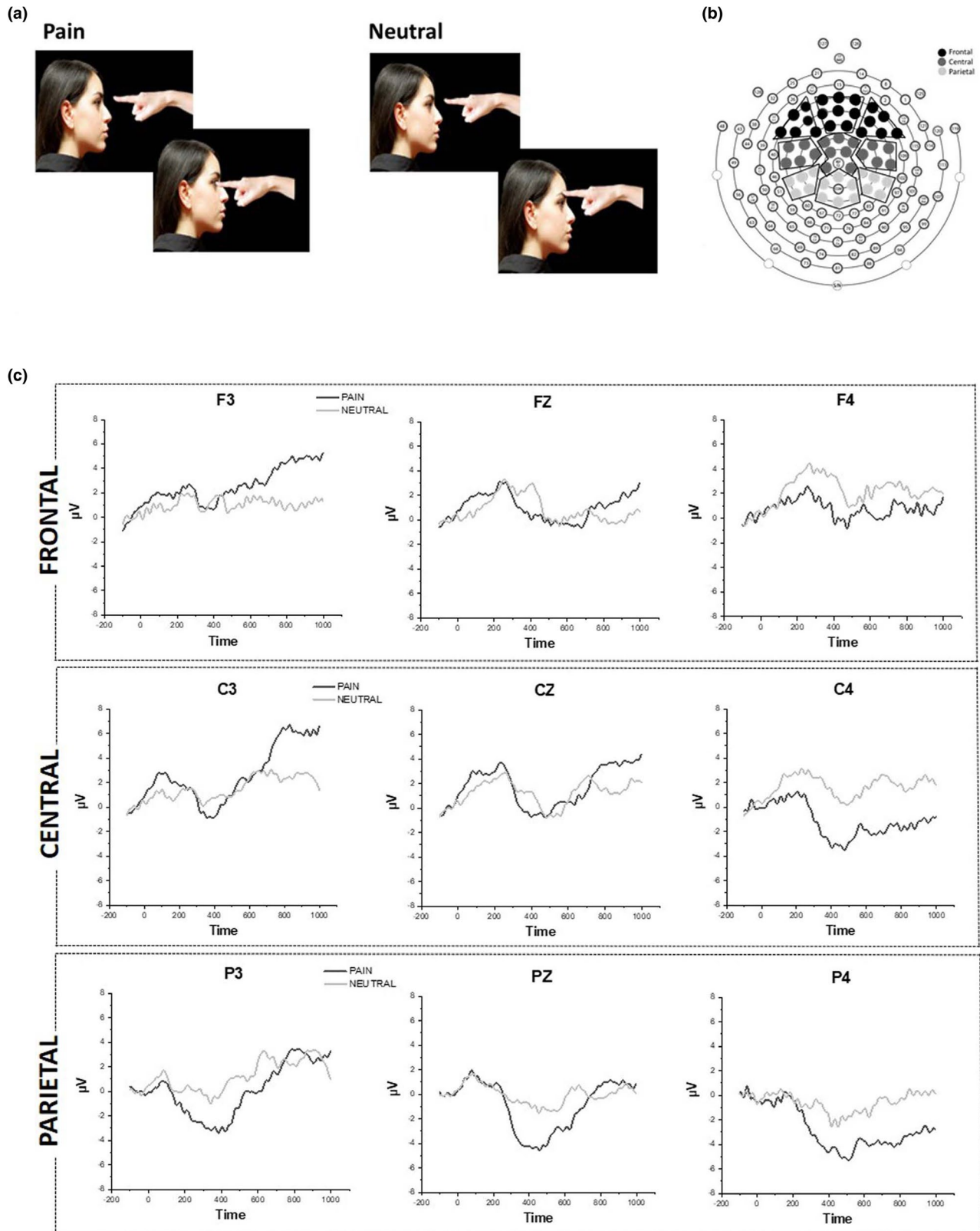
FIGURE 1 (a) The sequence of frames composing the stimuli representing the painful and neutral touch. (b) Schematic diagram of the 128 channels sensor layout showing the three clusters of electrodes (Frontal, Central, Parietal) in the left, right, and midline locations. (c) Average waveforms elicited at the onset of touch in each electrode cluster

high-frequency noise, and EMG activity. Furthermore, video recordings of the infants were coded off-line and served to exclude all trials in which the infant performed body movements, did not attend to the screen, or performed eye blinks and saccades. Of the remaining trials, individual channels containing artifacts were replaced using spherical spline interpolation. For each participant, average waveforms were generated within each experimental condition only if at least 8 artifact-free trials were overall available per condition. Averaged data were then re-referenced to the average reference. The mean number of trials was 12.5 (min 8–max 26) for the pain condition and 12.9 (min 8–max 23) for the neutral condition, with no differences across conditions, $t(19) = 0.583$, $p = 0.57$.

We analyzed differences in both the mid latency attentional Nc and later cognitive LPP ERP responses associated with attentional and evaluative processes related to pain processing (Cheng et al., 2014; Decety & Cowell, 2018). Analyses were conducted separately on the mean amplitude of the Nc (300–500 ms) and of the early (550–750 ms) and late (800–1000 ms) LPP components. The electrodes of the frontal cluster were 20, 23, 24, 27, 28, 34 (Left hemisphere, F3), 3, 116, 117, 118, 123, 124 (Right hemisphere, F4), and 4, 5, 10, 11, 12, 16, 18, 19 (Midline frontal, Fz). The Central cluster included sensors 29, 30, 35, 36, 41 (Left hemisphere, C3), 103, 104, 105, 110, 111 (Right hemisphere, C4), and 6, 7, 13, 31, 80, 106, 112 (Midline central, CZ). The parietal cluster was composed of sensors 37, 42, 47, 52, 53 (Left hemisphere, P3), 86, 87, 92, 93, 98 (Right

hemisphere, P4), and 54, 55, 61, 62, 78, 79 (Midline central, PZ; Figure 1b). The selected time windows and electrode locations were chosen based on the visual inspection and were similar to those used in previous ERP studies with infants and children (Cowell & Decety, 2015; Decety & Cowell, 2018; Grossmann et al., 2006; Xie et al., 2019). Topographical scalp potential maps for the Nc (300–500 ms), early LPP (550–750 ms), and late LPP (800–1000 ms) time windows in the painful and neutral stimuli are shown in Figure 2.

3 | RESULTS

3.1 | Nc (300–500 ms)

Visual inspection of the average waveforms has shown that painful touch elicited a prominent Nc (300–500 ms) throughout frontal, central, and parietal sites (Figure 1c). The rmANOVA with Electrode Cluster (Frontal, Central, Parietal), Lateralization (Right, Midline, Left), and Condition (Pain, Neutral) showed a significant main effect of Condition, $F(1,19) = 6.557$, $p = 0.02$, $\eta p2 = 0.257$. The Nc was greater in amplitude in response to painful (mean = −1.58 μV, SD = 3.40) compared to neutral touch (mean = 0.48 μV, SD = 4.23). There was also a significant three-way Electrode Cluster × Lateralization × Condition interaction, $F(4,76) = 2.916$, $p = 0.027$, $\eta p2 = 0.113$. Follow-up paired t-tests (Bonferroni-Holm corrected) revealed
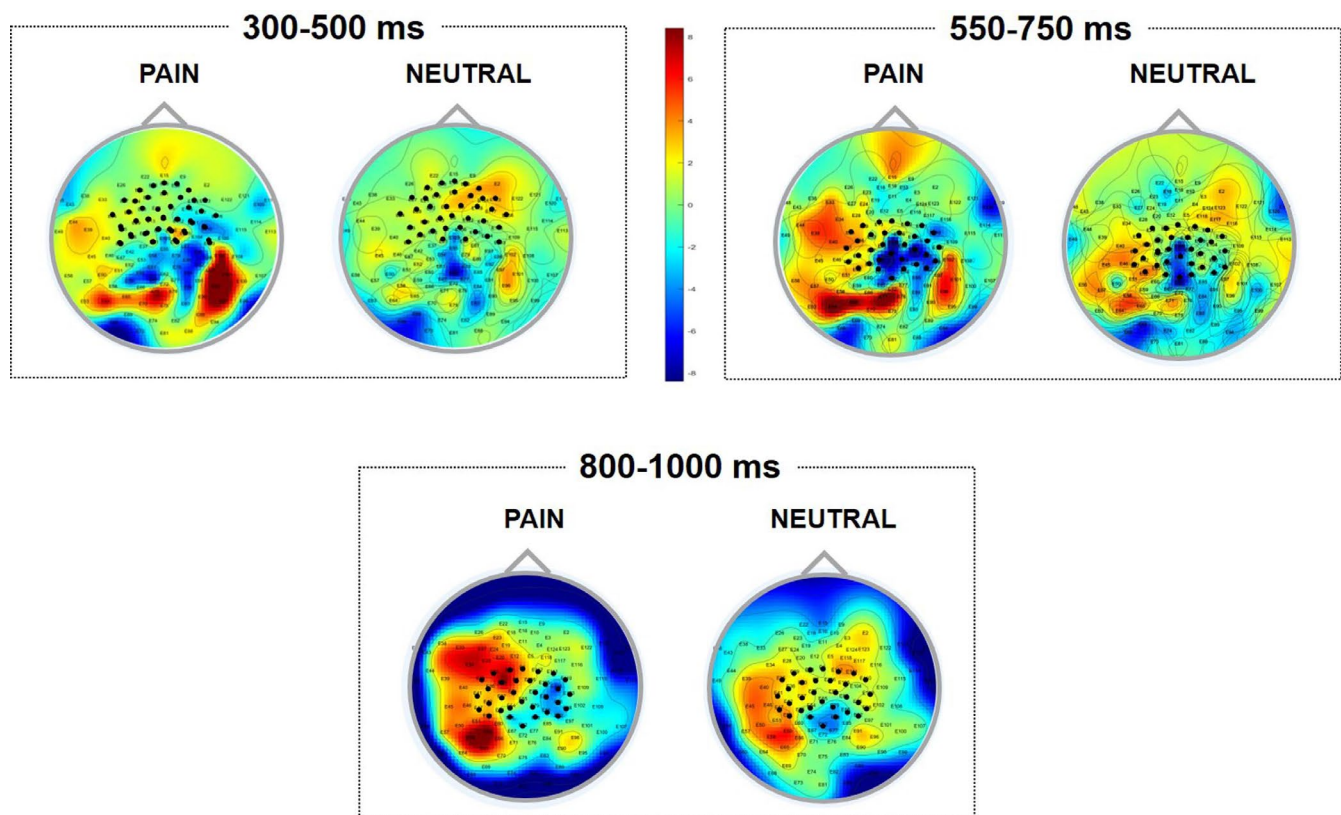

FIGURE 2 Topographical scalp potential maps in the 300–500 ms (Nc), 550–750 (early LPP), and 800–1000 (late LPP) time windows. Maps display positive values in red and negative values in blue, with maxima (+8 μV) and minima (−8 μV) of scalp potentials. Clusters where differential activity was found are highlighted in black

significant differences across conditions in the frontal and central electrode clusters only in the right hemisphere. Specifically, the Nc was larger in amplitude in response to painful (mean = −2.67 µV, SD = 4.98) compared to neutral touch (mean = 1.28 µV, SD = 5.95) in the right central cluster, $t(19) = 3.211$, $p = 0.005$. Greater activity of the Nc was also found in the right frontal cluster in response to painful (mean = 0.43 µV, SD = 5.60) compared to neutral touch (mean = 2.88 µV, SD = 3.08), $t(19) = 2.573$, $p = 0.038$. No other comparison reached significance (All $ps > 0.116$; see Table 1 for more information about the mean and SD of the Nc mean amplitude in the frontal and central cluster). Furthermore, there was a main effect of Electrode Cluster, $F(2,38) = 4.835$, $p = 0.003$, $\eta p2 = 0.270$, and a significant Electrode Cluster × Lateralization interaction, $F(4,76) = 3.379$, $p = 0.01$, $\eta p2 = 0.151$. Follow-up paired t-tests (Bonferroni-Holm corrected) showed only a significant difference in the parietal cluster between left (mean = −1.28 µV, SD = 4.04) and midline (mean = −4.15 µV, SD = 4.80) sensors, $t(19) = 2.590$, $p = 0.018$. No other comparison reached significance (All $ps > 0.248$).

3.2 | LPP early (550–750 ms) and late (800–1000 ms)

The rmANOVA on the mean amplitude of the early LPP (550–750 ms) with Electrode Cluster (Central, Parietal), Lateralization (Right, Midline, Left), and Condition (Pain, Neutral) as within-subject factors, showed a significant main effect of Condition, $F(1,19) = 4.564$, $p = 0.046$, $\eta p2 = 0.194$. The LPP was greater in amplitude in response to neutral (mean = 0.79 µV, SD = 3.57) compared to painful touch (mean = −0.89 µV, SD = 3.61; Figure 1c). Also, there was significant main effect of Lateralization, $F(2,38) = 3.884$, $p = 0.029$, $\eta p2 = 0.170$, being the early LPP greater in amplitude in the left (mean = 2.12 µV, SD = 5.58) compared to the midline cluster (mean = −1.07 µV, SD = 3.38), $t(19) = 2.814$, $p = 0.01$. No other comparison reached significance after Bonferroni-Holm correction (All $ps > 0.104$; Table 1).

The rmANOVA on the mean amplitude of the late LPP (800–1000 ms) showed a significant main effect of Lateralization, $F(2,38) = 5.068$, $p = 0.011$, $\eta p2 = 0.211$, being the late LPP greater in amplitude in the left (mean = 3.39 µV, SD = 5.76) compared to the midline cluster (mean = 0.41 µV, SD = 4.42), $t(19) = 2.904$, $p = 0.009$ and to the right cluster (mean = −0.58 µV, SD = 4.62), $t(19) = 2.523$, $p = 0.042$. No other comparison reached significance after Bonferroni-Holm correction (All $ps > 0.42$). Furthermore, there was a significant Condition × Lateralization interaction, $F(2,38) = 4.293$, $p = 0.027$, $\eta p2 = 0.173$. Follow-up paired t-tests (Bonferroni-Holm corrected) showed larger responses to the neutral (mean = 1.03 µV, SD = 6.32) compared to the painful stimulus (mean = −2.19 µV, SD = 5.07) over the right Hemisphere, $t(19) = 2.125$, $p = 0.047$. No other comparison reached significance (All $ps > 0.37$).

4 | DISCUSSION

Our study brings new interesting insights into the literature investigating the development of human empathy for pain. With a very simple but effective paradigm, the present study demonstrates that

TABLE 1 Means and SD of the Nc and of the early and late LPP activity expressed in µV in response to Painful and Neutral stimuli in the electrode clusters where significant differences were found

			Frontal			Central		
			F3	FZ	F4	C3	CZ	C4
Nc	Neutral	Mean	1.07	2.04	2.88	0.61	0.73	1.28
		SD	6.83	5.99	6.08	6.89	4.98	5.96
	Pain	Mean	1.53	0.49	0.43	−0.40	−0.26	−2.67
		SD	7.80	5.97	5.60	6.63	4.32	4.98

			Central			Parietal		
			C3	CZ	C4	P3	PZ	P4
Early LPP	Neutral	Mean	2.57	1.18	1.92	2.31	−2.34	−0.89
		SD	8.13	4.66	6.85	5.13	8.28	5.76
	Pain	Mean	2.78	0.48	−1.90	0.79	−3.63	−3.86
		SD	8.51	4.83	5.85	6.69	7.48	6.46

			Central			Parietal		
			C3	CZ	C4	P3	PZ	P4
Late LPP	Neutral	Mean	2.53	1.60	1.93	2.68	−2.08	0.14
		SD	8.94	5.98	8.29	6.79	8.51	5.44
	Pain	Mean	5.46	3.16	−1.32	2.91	−1.00	−3.06
		SD	7.51	4.99	5.99	8.54	7.96	6.18

already at 6 months of life, infants detect others' pain and differentiate at the neural level between painful and neutral tactile stimulations. Such differentiation appears over the Nc, a mid-latency ERP component indexing attentional orienting toward salient stimuli (Reynolds & Richards, 2005; Richards, 2001). The Nc is greater in amplitude in response to painful stimuli compared to neutral touches. A divergent activity is also visible in a subsequent component, the centro-parietal LPP, in both early and late time windows, which is involved in the evaluative processing of social signals.

A recent theory of empathy development proposes that emotional sharing (bottom-up process) is the first process to emerge, followed, later in development, by top-down cognitive processes (i.e., emotion regulation and perspective taking; Decety, 2010). This two-stage sequential processing of empathy is supported by fMRI studies showing the decreased activity of areas involved in affective arousal and somatovisceral resonance and increased activity of structures involved in the cognitive evaluation in response to harmful visual scenarios across development (Decety & Michalska, 2010). ERP studies have also shown a developmental trajectory in the activity of early and late components reflecting, respectively, emotional sharing (N2) and cognitive processes (LPP; Cheng et al., 2014). Our results provide novel support to such evidence, showing that painful stimuli affect the attentional mid-latency Nc in 6-month-old infants, resulting in greater amplitudes in response to painful compared to neutral scenarios. This differential activation indicates that infants pay more attention to the painful stimulation compared to the neutral one (indexed by the Nc) and possibly resonate with others' emotional experiences. As such, our results are in line with previous studies showing that infants share others' emotional and sensory experiences (Addabbo, Quadrelli, et al., 2020; Addabbo, Vacaru, et al., 2020; Meltzoff et al., 2018). Furthermore, our finding supports studies showing that infants are particularly attuned to others' distress and might show early forms of empathic concern for others (Davidov et al., 2013; Liddle et al., 2015; Roth-Hanania et al., 2011). Interestingly, differential activity between painful and neutral touch over the Nc is right-lateralized. Previous evidence with young children reported N2 differential responses to pain over centro-right electrode clusters (Decety et al., 2018). Our result also supports an ERP study exploring emotional processing in infancy (De Haan et al., 2004) and suggests that, in the present study, infants might have detected the emotional valence of the observed touch. Remarkably, the right hemisphere is considered to have a crucial role in emotional processing (Gainotti, 2019).

It is noteworthy that in literature there is a large consensus in the direction of the LPP activity in response to others' pain, which typically generates in adults (Coll, 2018), and in children from 4.5 to 9 years (Cheng et al., 2014) greater amplitudes in response to painful stimuli compared to neutral ones in central-parietal electrode sites. Differently from the above-mentioned literature, in our study, the LPP was greater in response to neutral compared to painful stimuli, with a right lateralization of such response over the late LPP time window. A right-lateralized LPP was also found in a previous study exploring infants' ERP responses to emotional body postures

(Missana et al., 2015). Increased activations of the LPP in response to neutral compared to painful stimuli were also found in a recent study conducted with younger children, aged from 3.5 to 5 years (Decety et al., 2018), showing that the process that underlies this late cognitive component might not be fully developed in the first years of life. The LPP is considered an index of top-down cognitive processes related to the evaluation of painful stimuli (Cheng et al., 2014; Fan & Han, 2008), and it has been linked to emotion regulation (Dennis & Hajcak, 2009). Emotion regulation is a crucial process that allows us to down-regulate negative arousal, to concentrate on the ongoing event, and respond adaptively and appropriately to stressful situations. Infants possess immature regulatory abilities, and they use some behavioral strategies, such as self-comforting behaviors (i.e., thumb sucking) or self-distraction (i.e., disengage their attention from negative stimuli), to deal with stressful events (Planalp, & Braungart-Rieker, 2015). Thus, the pattern of results over the LPP could reflect infants' reduced ability to down-regulate the arousal generated by the observation of painful stimuli, which, in turn, might have enabled infants' access to the cognitive resources essential for the evaluation of painful events. However, further studies are needed to explore the potential mechanism underlying the observed LPP response, also investigating whether individual differences in infants' self-regulative abilities have an impact on such late and cognitive ERP component. Overall, the present finding highlights the saliency of observed painful stimuli for young infants. Observing painful stimulations might have had a broad impact on infants' neural responses across the scalp due to an increase of attention allocation, possibly accompanied by a long-lasting increased level of emotional arousal.

However, our results not only shed light on the precursors of human empathy for others' pain but also enrich our understanding of infants' body knowledge and processing of observed touch. A myriad of early experiences are centered around touch, which is considered one of the very first senses to develop (Field, 2010). Already inside the womb, fetuses actively explore their bodies and the world around them (Myowa-Yamakoshi & Takeshita, 2006). As such, self-exploration contributes to the formation of body maps and of a rudimental sense of the body (Fagard et al., 2018), which then refines and enriches across development thanks to continued extensive touch activities (DiMercurio et al., 2018). Our results suggest that infants might have some knowledge about the sensitivity and delicacy of their body and that they might have detected the correspondence between their own and others' body parts (eye/eyebrow).

The high attrition rates and the limited number of trials represent a limitation of this study. However, it is important to note that the high drop-out rate found in our study is common in studies using electroencephalographic measures with infants (Stets et al., 2012). Regarding the small number of trials, it would be preferable, in future studies, to increase stimulus variability by using, for instance, different sets of stimuli depicting pain and neutral stimuli. This could help to keep infants' attention and interest in the displayed visual events for relatively longer periods of time.

In conclusion, our study is the first exploring infants' sensitivity to others' painful tactile sensations, showing a two sequential processing underlying pain observation in infancy, which affects both the Nc and the later, cognitive, stages of neural processing, indexed by the LPP. Self-exploration might have played a crucial role in infants' emerging ability to detect others' sensory experiences: infants' early knowledge about their own body, together with the emerging ability to share others' sensory experiences, might have boost an early sensitivity and attentional attunement to others' painful tactile sensations. This function might form the prerequisite for the development of more complex processes that characterize human empathy.

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CONFLICT OF INTEREST

We certify that there are no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria, and/or expert testimony).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author.

ORCID

Margaret Addabbo 🔟 https://orcid.org/0000-0002-8414-6853
Nadia Bolognini 🔟 https://orcid.org/0000-0002-2921-8658

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