

An ERP investigation of electrocortical responses in pain empathy from childhood through adolescence into adulthood

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Abstract

Only a few studies investigated the neurodevelopment of pain empathy. Here, the temporal dynamics of electrocortical processes in pain empathy during individual neurodevelopment from childhood through adolescence into adulthood, along with the moderation effect of top-down attention, were investigated using the event-related potential (ERP) technique. To investigate the role of top-down attention in empathy development, both A-P task and A-N task were conducted. In the A-P and A-N task, participants are instructed to judge whether the models in pictures were painful or non-painful and count the number of limbs in pictures, respectively. We found that compared to the adolescent and adult groups, the children group responded significantly worse, along with stronger neural responses in both tasks. Compared to the adolescent and adult groups, the differential amplitudes between painful and non-painful conditions of P2, N2 and P3 were significantly larger in the children group. Moreover, this P3 differential amplitude could only be modulated by age in the A-P task. These results suggest that the capacity to empathize has not yet attained complete development in these children. Significantly more attention resources were involuntarily attracted by the nociceptive cues in these children, which could also reflect the immaturity of empathy ability in these children.

Keywords: pain empathy; event-related potential; top-down attention; individual neurodevelopment

Introduction

Empathy is a complex and multifaceted ability to perceive or imagine the emotional states and thoughts of other people, and is the competence to appropriately respond to others' feelings (Netten *et al.*, 2015; Levy *et al.*, 2018). Empathy can induce prosocial behavior and cooperative behavior (Netten *et al.*, 2015). Therefore, it is considered a powerful ability for successful interpersonal interaction in everyday life and is often referred to as the 'social glue' in human relationships (Engen and Singer, 2013; Decety *et al.*, 2018).

Empathy, as per Gladstein's (1983) widely acknowledged theory, can be segregated into two separate constituents: affective empathy and cognitive empathy (Gladstein, 1983). Affective empathy, also known as emotional contagion, is the process in which affective sharing of the observed social and emotional cues of other people occurs (e.g. 'I feel what you feel') (Gladstein, 1983; Netten

et al., 2015; Peng *et al.*, 2019). Cognitive empathy is thought to pertain to the act of ascribing emotions or sentiments to individuals other than oneself, encompassing the identification and acknowledgement of the affective conditions of others, as well as the deduction of the mental states of others (e.g. 'I comprehend what you feel') (Gladstein, 1983; Schnell *et al.*, 2011).

Pain empathy, which is a typical form of empathy, is defined as the manner in which individuals perceive, identify and respond when they are observing other people in physical or social pain (Masten *et al.*, 2011; Coll, 2018). Similar to other format of empathy, pain empathy also involve both affective and cognitive components. Within laboratory settings, stimuli that featured nociceptive cues of other people were commonly delivered through visual or auditory channels (Kanel *et al.*, 2019; Meng *et al.*, 2019, 2023). Furthermore, in order to examine the impact of top-down attention on an individual's empathy process, two distinct

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tasks are typically administered: an explicit empathy task and an implicit empathy task (Meng et al., 2019, 2020). In the explicit empathy task (also known as the pain judgment task or the 'A-P task'), participants are instructed to judge the level of pain experienced by the models depicted in pictures, which usually requires participants to direct their attention to nociceptive cues. In the implicit empathy task, participants are required to count the number of hands, feet, legs or forearms depicted in pictures of body pain (i.e. a number-counting task) or rate the attractiveness of models in pictures of face pain (i.e. an attractiveness judgment task). This directs participants' attention away from the models' feelings and potential nociceptive cues in the pictures and is also known as the 'A-N task'. The evaluation of explicit and implicit empathy in participants can be achieved by administering these two types of tasks as recommended (Gu et al., 2010). Explicit empathy is generally perceived as a deliberate and regulated cognitive process, whereas implicit empathy is commonly viewed as a spontaneous phenomenon that operates beyond the boundaries of conscious perception (Yan and Han, 2008; Meng et al., 2019).

To explicate the cerebral processes and computational mechanisms that underlie empathy, contemporary neuroimaging techniques have been employed in prior research endeavors (Schnell et al., 2011; Coll, 2018). While the functional magnetic resonance imaging (fMRI) technique could be used to reveal the cortical regions responsible for empathy, the event-related potential (ERP) technique is widely used to explore the temporal dynamics of neural responses to nociceptive cues depicting various levels of pain in others (Yan and Han, 2008). Results from ERP studies suggest that empathy for pain can be divided into two distinct neural processing stages: (i) an earlier automatic processing stage, which includes the ERP components N1, P2 and N2 and reflects the perception of others' pain and the sharing of others' feelings, (ii) a later cognitive evaluation/appraisal stage, which includes the ERP components P3 and Late Positive Component (LPC) and involves further evaluations of others' feelings and action preparations (Peng et al., 2019). The N1, P2 and N2 ERP components are closely related to the affective aspect of pain empathy, while the P3 and LPC components are associated with the cognitive aspect of pain empathy (Li et al., 2019; Meng et al., 2019). An examination of the collective findings from ERP investigations on pain empathy has indicated that the posterior P3 and LPC display discernment in response to the observation of pain in others (Coll, 2018). Specifically, their amplitudes exhibit a significant increase when participants are exposed to painful stimuli. In contrast, the early N1 and N2 components do not exhibit a consistent correlation with vicarious pain observation. Moreover, previous studies have shown that the amplitudes of ERP components evoked by painful and non-painful stimuli, as well as the amplitude differences between these two types of stimuli, can be modulated by task demands (e.g. pain judgment vs number-counting) and contextual reality (Yan and Han, 2008; Meng et al., 2019, 2020). For example, the amplitude variations observed in ERP waveforms generated by painful and non-painful images are often lessened when task requirements impede the processing of pain stimuli and participants' attention is diverted from the nociceptive cues (Li et al., 2019).

From a developmental perspective, the two components of empathy (i.e. affective empathy and cognitive empathy) develop along different trajectories (Decety, 2010; Schwenck et al., 2014). The behavioral responses related to affective empathy appear during the very early stages of human ontogeny (Haviland and Lelwica, 1987; Imuta et al., 2016). As an instance, newborns exhibit contagious crying behavior when they hear the cries of

other individuals. Nonetheless, these infants and toddlers lack the cognitive ability to comprehend that their melancholic emotions stem from the suffering of another individual (Dondi et al., 1999). During the course of childhood, physiological maturation leads to the gradual emergence of the capacity to differentiate between self-inflicted pain and pain experienced by others. This developmental process also fosters an understanding of the reasons for others' sadness, thereby facilitating rapid cognitive empathy growth. Although researchers have extensively studied the emergence of empathy through the use of psychological scales and behavioral paradigms, there has been a significant lack of research on the underlying neural maturation of this process, particularly through the utilization of ERP/Electroencephalography (EEG) techniques. In a related study, Cheng et al. (2014) analyzed the ERP components evoked by short visual animations depicting painful situations in typically developing children and young adults (Cheng et al., 2014). According to their findings, there was a decline in the amplitude of the N2 component's difference wave between pain and painful stimuli, which was linked to age. On the other hand, the LPC's difference wave showed an increase in amplitude that was also linked to age. The researchers concluded that these age-related changes may indicate a decrease in affective sharing/arousal and an increase in cognitive appraisal as empathy develops. Nonetheless, it is our view that Cheng et al. (2014) suffer from no less than two limitations. Firstly, the dynamic animations used to evoke empathetic responses consist of three consecutive pictures, with durations of 1000 ms, 50 ms and 1000 ms, respectively. Upon inspection of the example pictures presented in Figures 1 and 2 of Cheng et al. (2014) study, we noticed that the nociceptive cues were not synchronized with a specific location in the picture. This could potentially lead to confusing results regarding the temporal dynamics of empathy processing. Secondly, only an explicit empathy task was conducted; thus, it failed to reveal the role of top-down attention on individuals' empathy development.

In the current study, the temporal dynamics of neural processes related to empathy during individual development from childhood through adolescence into adulthood were investigated using ERP technique. Moreover, to investigate the role of top-down attention in individuals' empathy development, both explicit empathy tasks and implicit empathy tasks were conducted. Based on prior behavioral and neural evidence regarding the development of empathy and the role of top-down attention in empathetic responses, we have the following hypotheses. Since the empathy ability has not yet reached maturity in childhood, children may have difficulty judging whether others are in a painful situation. As a result, they may respond slower and make more errors in both the pain judgment task and the number-counting task. These difficulties can significantly alter their ERP responses to painful stimuli. Moreover, the top-down attention on the nociceptive cue should also modulate children's neural response to the stimuli. This study aims to enhance our comprehension of the temporal dynamics of neural processes associated with empathy as individuals develop over their lifespan, as well as the influence of top-down attention on the processing of second-hand nociceptive information in human development.

Material and methods

Participants

A priori power analysis conducted using the G*Power 3 revealed that 45 participants were required to reach a good statistical

power of 0.95 to detect median-sized ($f=0.25$) effects with an alpha value of 0.05 for a three-way repeated-measures analysis of variance (ANOVA) with two within-participant factors of 'condition' (i.e. painful vs non-painful) and 'task' (i.e. A-P task and A-N task), and one between-participants factor of 'group' (i.e. children, adolescent and adult) as independent variables. A total of 120 healthy, right-handed individuals between the ages of 8 and 24 participated in the study. All participants were divided into three age groups: (i) the children group (16 females, 16 males; mean age = 10.28 years, s.d. = 0.68 years; aged from 9 to 11 years); (ii) the adolescent group (17 females, 15 males; mean age = 16.19 years, s.d. = 1.31 years; aged from 15 to 17 years); and (iii) the adult group (27 females, 29 males; mean age = 20.31 years, s.d. = 1.53 years; aged from 19 to 24 years). The individuals in the children group, adolescent group and adult group were recruited through advertisements at the local primary school, middle school and university, respectively. The entire cohort of participants exhibited either typical or corrected-to-typical eyesight. Additionally, none of them had a history of psychiatric or neurological disorders, recent medication that could potentially affect brain function or substance abuse. Demographic variables, including socioeconomic status and ethnicity, show no significant differences. The participants or their parents provided informed consent for the current study. The procedures of the current study were approved by the local ethics committee of Henan University and conducted in accordance with the principles of the Declaration of Helsinki.

Materials

A total of 136 pictures, consisting of 68 painful and 68 non-painful pictures, from the Empathy for Limb Pain Picture Database (EPSS-Limb) (Meng et al., 2023), were selected and used in the current study. The picture database has previously been validated and used in published studies (Meng et al., 2019). Each picture portrayed a common occurrence that could happen in daily life. The painful images featured a model experiencing pain in either one or both hands, feet, legs or forearms, such as a hand being pricked by a needle or a foot being penetrated by a syringe. The non-painful images were similar in nature but did not exhibit any painful elements, such as a needle being used for sewing or a foot being touched by a pencil. The luminance, contrast and color of the painful and non-painful limb pictures were matched. Each picture was 9×6.76 cm (width \times height) and 100 pixels per inch. A total of 75 pictures showed one hand, foot, leg or forearm (33 painful and 42 non-painful scenes), and 59 pictures showed two hands, feet, legs or forearms (33 painful and 26 non-painful scenes). Two pairs of example pictures are shown in Figure 1.

Previous studies have shown that: (i) the pain intensity ratings of painful pictures were significantly higher than those of non-painful pictures; (ii) painful pictures induced significantly more negative feelings than non-painful pictures; (iii) painful pictures were significantly more exciting than non-painful pictures; (iv) painful pictures were rated as more out of control than non-painful stimuli (Meng et al., 2023). These results were also validated by the present study. Here, after the formal experiment and EEG recording, all participants in the three groups were asked to rate the intensity of others' pain in the pictures based on a 9-point pain intensity scale (1 = no sensation, 4 = pain threshold, 9 = most intense pain imaginable) and evaluate their subjective emotional reactions to these pictures using a 9-point emotion scale (1 = neutral, 5 = moderately unhappy, 9 = extremely unhappy). The mean scores and s.d. of subjective report scores

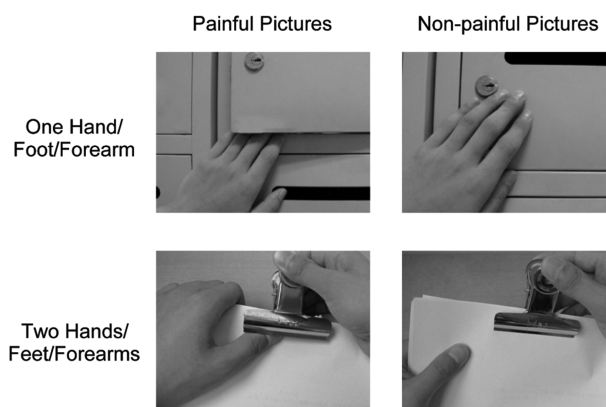


Fig. 1. Examples of one hand, foot, leg or forearm picture (painful picture: upper-left panel; non-painful picture: upper-right panel) and two hands, feet, legs or forearms pictures (painful picture: lower-left panel; non-painful picture: lower-right panel).

(i.e. pain intensity ratings and emotional reactions) for the painful and non-painful pictures of three participant groups are shown in Table 1. For all three groups, participants rated painful pictures significantly higher in pain intensity than non-painful pictures (the children group: $t[31] = 10.59$, $P < 0.01$; the adolescent group: $t[31] = 9.13$, $P < 0.01$; the adult group: $t[55] = 20.44$, $P < 0.01$). Moreover, all three groups of participants judged the painful pictures with significantly more negative emotional reactions than the non-painful pictures (the children group: $t[31] = 5.92$, $P < 0.01$; the adolescent group: $t[31] = 7.00$, $P < 0.01$; the adult group: $t[55] = 20.98$, $P < 0.01$).

Experimental procedures

The participants were seated in an environment with a regulated temperature of approximately 25°C and minimal sound, with a 21.5-inch color monitor placed in front of them. The participants were instructed to maintain their attention on the stimuli presented on the screen throughout the experiment.

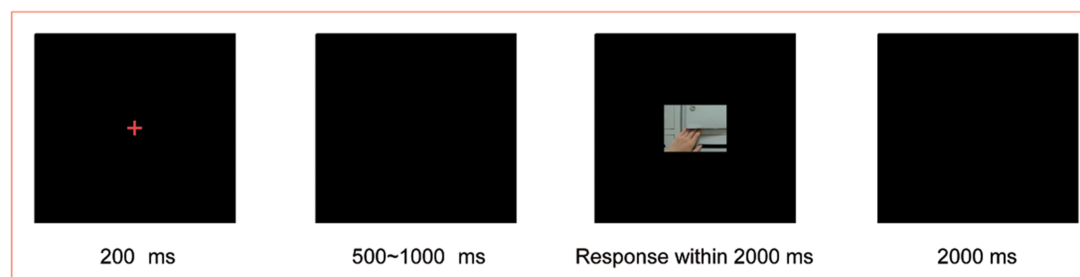
The entire experiment consisted of two sessions involving two different tasks: the attention-to-pain-cue task (A-P task) and the attention-to-non-pain-cue task (A-N task). In the A-P task, participants were required to judge whether the models in the depicted scenes were experiencing pain or not, while in the A-N task, participants were instructed to count the number of hands, feet or forearms in the pictures, responding by pressing a key on the keyboard (i.e. 'F' and 'J') with their right hand. Note that the order of the two experimental tasks (i.e. the A-P task and the A-N task) was counterbalanced among participants.

A representation of the pipeline for each trial in the A-P task and the A-N task is provided in Figure 2.

For the A-P task, at the start of a specific trial, a red fixation cross was presented for 200 ms in the center of a black screen, followed by a blank interval (randomly varied from 500 ms to 1000 ms). After this blank interval, one of the selected pictures, either painful or non-painful picture, was presented in the center of the black screen. The participants were instructed to judge whether the picture was painful or non-painful as quickly and accurately as possible within 2000 ms. The picture disappeared from the screen as soon as the participants responded by pressing 'F' or 'J' on the keyboard. The interval between two consecutive trials was 2000 ms. Prior to the formal A-P task, a training session was conducted during which each participant could familiarize themselves with the experimental procedures. This

Table 1. The mean \pm SE of subjective report scores (i.e. pain intensity ratings and emotional reactions) of the painful and non-painful pictures for three groups of participants

| | Children (N = 32) | | Adolescent (N = 32) | | Adult (N = 56) | |
|------------------------|-------------------|-----------------|---------------------|-----------------|-----------------|-----------------|
| | Painful | Non-painful | Painful | Non-painful | Painful | Non-painful |
| Pain intensity ratings | 5.61 \pm 0.32 | 1.90 \pm 0.19 | 5.09 \pm 0.34 | 1.79 \pm 0.19 | 6.14 \pm 0.23 | 1.54 \pm 0.09 |
| Emotional reactions | 5.03 \pm 0.38 | 2.47 \pm 0.27 | 4.65 \pm 0.38 | 1.87 \pm 0.16 | 6.35 \pm 0.21 | 1.79 \pm 0.12 |

**Fig. 2.** Pipeline of a single trial in the A-P task or A-N task. In the A-P task, participants were required to judge whether the pictures were painful or non-painful, while in the A-N task, participants were instructed to count the number of hands, feet, legs or forearms in the pictures.

training session consisted of six trials, during which three painful pictures and three non-painful pictures were selected from the picture database. These particular pictures were excluded from the formal experiment. Thus, 65 painful pictures and 65 non-painful pictures were used in the formal A-P task, resulting in 65 painful trials and 65 non-painful trials. All of these pictures were presented in a random order. The stimulus presentation was controlled using the E-Prime program.

The experimental procedures of each trial in the A-N task were identical to those of the A-P task, except that participants were required to count the number of hands, feet, legs and forearms in the pictures as accurately and quickly as possible.

EEG data collection

The EEG data were collected from 62 Ag-AgCl scalp electrodes placed according to the international 10–10 system (Brain Products GmbH, Munich, Germany; pass band: direct current [DC] to 280 Hz; sampling rate: 1000 Hz; online reference: electrode Fz; ground: electrode FPz). The impedances of all the electrodes were kept ≤ 10 k Ω throughout EEG recording.

Behavioral data analysis

The accuracy rate (ACC) and reaction time (RT) for each condition (painful or non-painful), each task (A-P task and A-N task) and each participant were computed. Note that trials were excluded from analyses when the RTs deviated by 2 or more s.d. from an individual participant's overall mean RT or when the participant made an incorrect response. To discount possible criterion shifts or speed-accuracy-trade-off effects, the inverse efficiency score (IES) for each condition, task and participant was also computed. As an adjusted RT measure, IES is derived by dividing RT by its corresponding ACC (Meng et al., 2019; Statsenko et al., 2020).

EEG data pre-processing

For each participant, the EEG data of each task were pre-processed offline using open-source toolbox EEGLAB (Delorme and Makeig, 2004) and custom-written scripts in MATLAB (The MathWorks, Natick, MA) through the following steps. The pipelines for EEG pre-processing for the A-P task and the A-N task were identical.

The raw continuous EEG data were band-pass filtered between 0.5 and 30 Hz via a finite impulse response filter, downsampled to 250 Hz and re-referenced to the bilateral mastoid electrodes. EEG epochs of the painful and non-painful condition were extracted using a time window of 3000 ms (1000 ms pre-stimulus and 2000 ms post-stimulus relative to the onset of painful/non-painful pictures) and baseline-corrected by subtracting the mean EEG data value of the pre-stimulus interval. Trials, in which RT deviated by more than two s.d. from an individual participant's overall mean RT or the participant made a wrong response, were excluded from further analysis. For the remaining EEG epochs, 'bad electrodes' were identified via visual inspection and interpolated using a spherical spline method. EEG epochs with large drift were deleted. EEG epochs contaminated by eye blinks and movements, electromyography, electrocardiography or any non-physiological artifacts were corrected using an independent component analysis (ICA) algorithm. Finally, EEG epochs with amplitude values exceeding ± 100 μ V at any electrode were rejected.

During EEG data pre-processing, the number of interpolated channels (mean \pm s.d.) in the children's group, adolescent group and adult group were 4.3 ± 0.8 , 4.8 ± 0.6 , and 4.5 ± 0.9 , respectively. The number of deleted epochs (mean \pm s.d.) in the children's group, adolescent group and adult group were 20.4 ± 3.8 , 14.3 ± 3.6 , and 16.5 ± 4.9 , respectively. The number of remaining epochs did not differ significantly between the three groups ($P > 0.05$).

ERP waveforms analysis

To analyze the ERP waveforms, the pre-processed EEG epochs of each condition, task and participant were further segmented into 1200 ms time-windows (200 ms pre-stimulus and 1000 ms post-stimulus) and baseline-corrected using the pre-stimulus time interval. EEG epochs belonging to the same experimental condition were averaged, resulting in single-participant ERP waveforms for each condition, task and electrode. Single-participant ERP waveforms were subsequently averaged to obtain group-level grand average waveforms. Group-level grand average scalp topographies for certain time intervals were computed by spline interpolation.

Table 2. The mean \pm SE of behavioral measures of the painful and non-painful pictures for three groups of participants in the A-P task and A-N task

| | | | RT (ms) | ACC (%) | IES (ms) |
|----------|------------|-------------|---------------------|------------------|---------------------|
| A-P task | Children | Non-painful | 1088.34 \pm 22.54 | 78.51 \pm 1.57 | 1413.29 \pm 52.42 |
| | | Painful | 1004.14 \pm 25.43 | 85.5 \pm 1.48 | 1198.49 \pm 53.29 |
| | Adolescent | Non-painful | 874.92 \pm 23.77 | 80.82 \pm 2.18 | 1137.94 \pm 74.39 |
| | | Painful | 804.84 \pm 18.25 | 88.51 \pm 0.85 | 912.53 \pm 23.18 |
| | Adult | Non-painful | 861.81 \pm 15.00 | 84.97 \pm 0.98 | 1020.36 \pm 19.96 |
| | | Painful | 797.14 \pm 17.64 | 89.95 \pm 0.90 | 897.78 \pm 29.09 |
| A-N task | Children | Non-painful | 926.07 \pm 20.53 | 88.13 \pm 0.88 | 1056.02 \pm 28.52 |
| | | Painful | 985.61 \pm 20.90 | 80.87 \pm 0.96 | 1227.65 \pm 34.63 |
| | Adolescent | Non-painful | 731.76 \pm 15.54 | 90.10 \pm 0.99 | 815.40 \pm 20.03 |
| | | Painful | 770.61 \pm 18.06 | 83.41 \pm 1.16 | 931.01 \pm 27.29 |
| | Adult | Non-painful | 705.86 \pm 14.96 | 90.85 \pm 0.95 | 783.16 \pm 19.74 |
| | | Painful | 753.77 \pm 16.10 | 83.32 \pm 0.92 | 912.08 \pm 22.87 |

Table 3. The mean \pm SE of amplitudes of ERP components of the painful and non-painful pictures for three groups of participants in the A-P task and A-N task

| | | | N1 (μ V) | P2 (μ V) | N2 (μ V) | P3 (μ V) | LPC (μ V) |
|----------|------------|-------------|-------------------|------------------|------------------|------------------|------------------|
| A-P task | Children | Non-painful | -10.24 \pm 1.24 | 3.76 \pm 1.49 | -6.91 \pm 1.32 | 10.41 \pm 1.55 | 8.73 \pm 0.95 |
| | | Painful | -10.76 \pm 1.26 | 4.54 \pm 1.34 | -8.51 \pm 1.24 | 12.70 \pm 1.47 | 10.52 \pm 1.06 |
| | Adolescent | Non-painful | -4.51 \pm 0.84 | -0.12 \pm 0.56 | -4.37 \pm 1.09 | 4.80 \pm 0.91 | 2.79 \pm 0.61 |
| | | Painful | -4.53 \pm 0.89 | -0.52 \pm 0.57 | -5.28 \pm 1.21 | 5.31 \pm 0.93 | 4.33 \pm 0.76 |
| | Adult | Non-painful | -5.00 \pm 0.43 | 2.40 \pm 0.52 | -6.41 \pm 0.68 | 6.24 \pm 0.56 | 3.52 \pm 0.37 |
| | | Painful | -4.99 \pm 0.45 | 1.79 \pm 0.53 | -7.11 \pm 0.74 | 6.80 \pm 0.55 | 4.62 \pm 0.41 |
| A-N task | Children | Non-painful | -11.06 \pm 1.13 | 4.94 \pm 1.37 | -6.26 \pm 1.13 | 10.48 \pm 1.45 | 7.74 \pm 1.00 |
| | | Painful | -11.31 \pm 1.15 | 4.74 \pm 1.48 | -7.60 \pm 1.37 | 10.97 \pm 1.58 | 8.08 \pm 1.14 |
| | Adolescent | Non-painful | -4.11 \pm 0.63 | 0.12 \pm 0.51 | -3.54 \pm 0.81 | 2.93 \pm 0.77 | 1.33 \pm 0.40 |
| | | Painful | -3.95 \pm 0.57 | -0.07 \pm 0.51 | -4.24 \pm 0.93 | 3.22 \pm 0.85 | 1.65 \pm 0.47 |
| | Adult | Non-painful | -4.82 \pm 0.45 | 1.43 \pm 0.53 | -6.11 \pm 0.72 | 3.91 \pm 0.54 | 1.88 \pm 0.37 |
| | | Painful | -4.74 \pm 0.44 | 1.21 \pm 0.56 | -6.39 \pm 0.68 | 3.82 \pm 0.53 | 1.93 \pm 0.40 |

Through visual inspection of grand average ERP waveforms of both the A-P task and the A-N task, five ERP components were identified: N1, P2, N2, P3 and the LPC. For the A-P task and A-N task, the amplitudes of N1, P2, N2, P3 and LPC were evaluated as the mean amplitude within the time windows of 120–160 ms, 160–210 ms, 210–280 ms, 290–400 ms and 450–800 ms, respectively.

Based on the visual inspection of scalp distributions of these ERP components in the A-P task and A-N task, we could find that: (i) N1 was largest over the frontal electrodes; (ii) P2 and P3 were largest over the parietal-occipital electrodes; (iii) N2 was largest over the frontal-central electrodes; (iv) LPC was largest over the parietal electrodes. Then, electrodes of interest (EOIs) were defined according to this information. The EOIs for the ERP component N1 were F3, F4 and Fz. The EOIs for the ERP components P2 and P3 were PO3, PO4 and POz. The EOIs for the ERP component N2 were FC3, FC4 and FCz. The EOIs for the ERP component LPC were P3, P4 and Pz.

For each condition, task and participant, the amplitude of each ERP component was defined as the mean amplitude across its ROI electrodes and time window.

Statistical tests

In order to investigate the moderating effect of participants' age, stimuli type and top-down attention on behavioral and neural responses, a three-way repeated-measures ANOVA was conducted on each kind of behavioral metric (i.e. RT, ACC and IES) and each ERP component. In the ANOVA, two within-participant

factors of 'condition' (i.e. painful vs non-painful) and 'task' (i.e. A-P task and A-N task), and one between-participants factor of 'group' (i.e. children, adolescent and adult) were included as independent variables. The degrees of freedom for F-ratios were corrected according to the Greenhouse-Geisser method.

Results

Behavioral results

The mean values and SEs of three types of behavioral metrics (i.e. RT, ACC and IES) for painful and non-painful pictures are presented in Table 2 for the three participant groups in the A-P task and A-N task.

The ANOVA conducted on RT found the following results (Figure 3). The main effect of task was significant, $F(1,117) = 61.06$, $P < 0.001$, $\eta_p^2 = 0.343$. The RT in A-N task was significantly shorter than that in A-P task. The main effect of condition was significant, $F(1,117) = 9.68$, $P < 0.01$, $\eta_p^2 = 0.076$. The RT of painful pictures was significantly shorter than that of non-painful pictures. The main effect of group was significant, $F(2,117) = 59.02$, $P < 0.001$, $\eta_p^2 = 0.502$. Further post-hoc tests revealed that the RTs of the children's group were significantly longer than those of the adolescent and adult groups, whereas a significant difference could not be found between the RTs of the adolescent and adult groups. The interaction effect between task and group, along with the interaction effect between condition and group, were not significant, $F_s < 1$, $ps > 0.05$. The interaction effect between task and condition was significant, $F(1,117) = 251.99$, $P < 0.001$, $\eta_p^2 = 0.683$. Further simple effect analysis revealed that in the A-P task, the

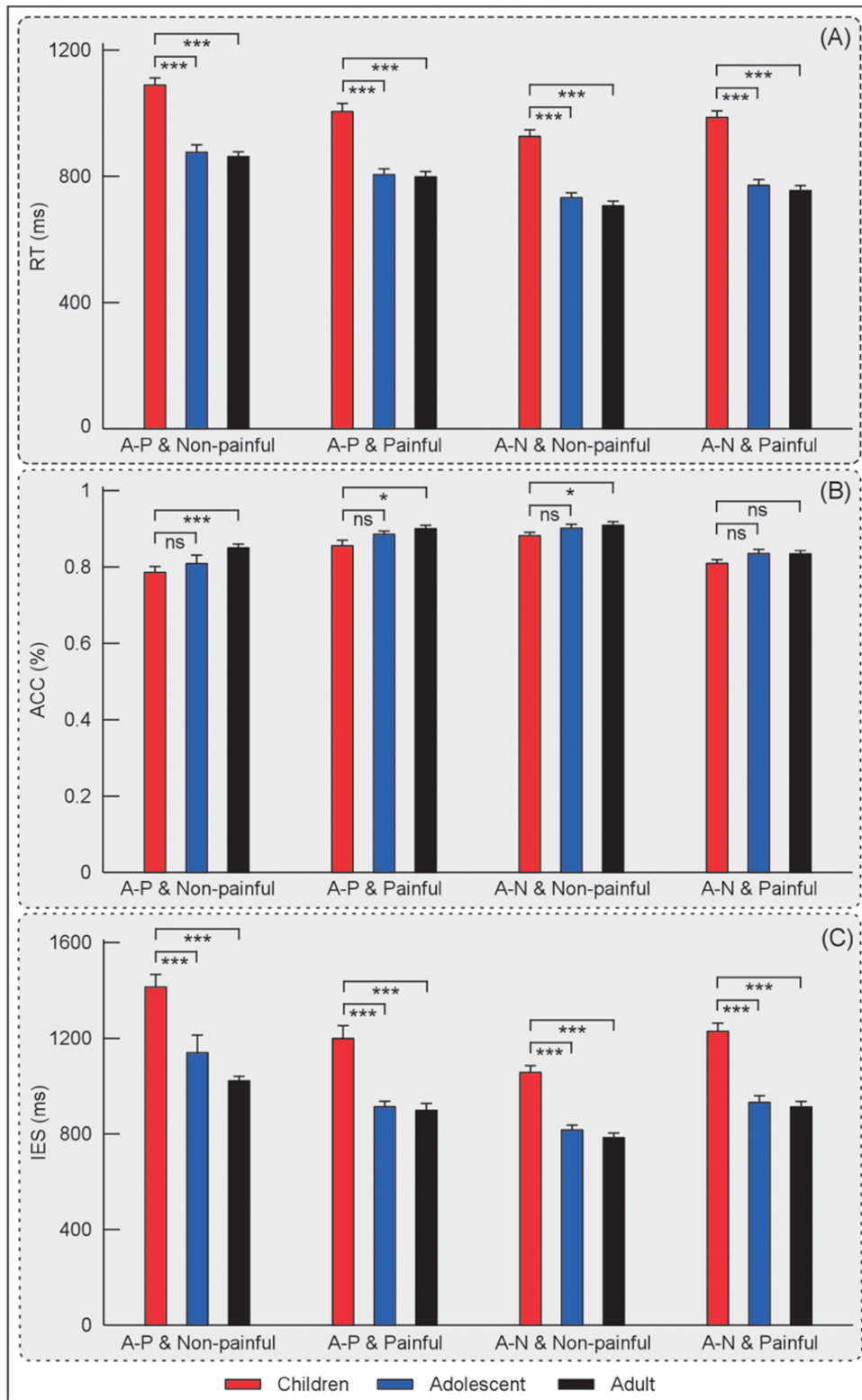


Fig. 3. The behavioral measures (panel A: RT; panel B: ACC; panel C: IES) of the non-painful and painful pictures in the A-P task and A-N task of the three groups of participants. The error bar represents one SE (ns: non-significant; *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$).

RT of painful pictures was significantly shorter than that of non-painful pictures, whereas in the A-N task, the RT of painful pictures was significantly longer than that of non-painful pictures. The interaction effect between task, condition and group was not significant, $F(2117) = 1.900, P > 0.05$.

The ANOVA conducted on ACC found the following results (Figure 3). The main effect of task was significant, $F(1117) = 5.313, P < 0.05, \eta_p^2 = 0.043$. The ACC in A-N task was significantly higher than that in A-P task. The main effect of condition was not significant, $F(1117) = 0.24, P > 0.05$. The main effect of group was

significant, $F(2117) = 7.66$, $P < 0.01$, $\eta_p^2 = 0.116$. Further post-hoc tests revealed that the ACC of the children's group was significantly lower than that of the adolescent and adult groups, whereas a significant difference could not be found between the ACC of the adolescent and adult groups. The interaction effect between task and group, along with the interaction effect between condition and group, were not significant, $F_s < 3$, $p_s > 0.05$. The interaction effect between task and condition was significant, $F(1117) = 125.374$, $P < 0.001$, $\eta_p^2 = 0.517$. Further simple effect analysis revealed that in the A-P task, the ACC of painful pictures was significantly higher than that of non-painful pictures, whereas in the A-N task, the ACC of painful pictures was significantly lower than that of non-painful pictures. The interaction effect between task, condition and group was not significant, $F(2117) = 0.294$, $P > 0.05$.

The ANOVA conducted on IES found the following results (Figure 3). The main effect of task was significant, $F(1117) = 58.287$, $P < 0.001$, $\eta_p^2 = 0.333$. The IES in A-N task was significantly shorter than that in A-P task. The main effect of condition was not significant, $F(1117) = 2.805$, $P > 0.05$. The main effect of group was significant, $F(2117) = 47.16$, $P < 0.001$, $\eta_p^2 = 0.446$. Further post-hoc tests revealed that the IESs of the children's group were significantly longer than those of the adolescent and adult groups, whereas a significant difference could not be found between the IESs of the adolescent and adult groups. The interaction effect between task and group, along with the interaction effect between condition and group, were not significant, $F_s < 2$, $p_s > 0.05$. The interaction effect between task and condition was significant, $F(1117) = 115.205$, $P < 0.001$, $\eta_p^2 = 0.496$. Further simple effect analysis revealed that in the A-P task, the IES of painful pictures was significantly shorter than that of non-painful pictures, whereas in the A-N task, the IES of painful pictures was significantly longer than that of non-painful pictures. The interaction effect between task, condition and group was not significant, $F(2117) = 1.977$, $P > 0.05$.

ERP results

The grand-average ERP waveforms across the EOIs, along with the grand-average topographical maps and statistical results, are shown in Figures 4 to Figure 8. The mean values and SEs of amplitudes of ERP components for painful and non-painful pictures are presented in Table 3 for the three participant groups in the A-P task and A-N task.

Statistical tests performed on the amplitudes of the ERP components yielded the following findings.

Firstly, for ERP component N1, we found the following results. The main effects of task and condition were not significant, $F_s < 1$, $p_s > 0.05$. The main effect of group was significant, $F(2117) = 29.02$, $P < 0.001$, $\eta_p^2 = 0.332$. Further post-hoc test revealed that the N1 amplitude of the children group was significantly more negative than those of the adolescent and adult groups, whereas significant difference could not be found between the N1 amplitude of adolescent group and that of adult group. The interaction effects between task and group, between condition and group and between task and condition were not significant. The interaction effect between task, condition and group was also not significant.

Secondly, for ERP component P2, we found the following results. The main effects of task and condition were not significant, $F_s < 2$, $p_s > 0.05$. The main effect of group was significant, $F(2117) = 7.358$, $P < 0.01$, $\eta_p^2 = 0.332$. Further post-hoc test revealed that the P2 amplitude of the children group was significantly more positive than those of the adolescent and adult groups. The interaction effects between task and group, and between

task and condition were not significant, $F_s < 1$, $p_s > 0.05$. The interaction effect between condition and group was significant, $F(2117) = 4.025$, $P < 0.05$, $\eta_p^2 = 0.064$. The simple effect analysis showed that the P2 amplitude difference between painful and non-painful pictures of the children group was significantly more positive than those of the adolescent and adult groups. The interaction effect between task, condition and group was marginally significant, $F(2117) = 3.039$, $P = 0.052 > 0.05$, $\eta_p^2 = 0.049$. Further analyses showed that the interaction effect between condition and group was significant in the A-P task, whereas the interaction effect between condition and group was not significant in the A-N task. Simple effect analysis showed that in the A-P task, the P2 amplitude difference between painful and non-painful pictures of the children group was significantly more positive than those of the adolescent and adult groups.

Thirdly, for ERP component N2, we found the following results. The main effect of task was marginally significant, $F(1117) = 3.046$, $P = 0.08 > 0.05$. The N2 amplitude in the A-P task was more negative than that in the A-N task. The main effect of condition was significant, $F(1117) = 39.48$, $P < 0.001$, $\eta_p^2 = 0.252$. This was caused by the fact that the N2 amplitude of painful pictures was significantly more negative than that of non-painful pictures. The main effect of group was marginally significant, $F(2117) = 2.637$, $P = 0.07 > 0.05$, $\eta_p^2 = 0.043$. Further post-hoc test revealed that the N2 amplitude of the children group was significantly more negative than those of the adolescent and adult groups, whereas significant difference could not be found between the N2 amplitude of adolescent group and that of adult group. The interaction effects between task and group, and between task and condition were not significant, $F_s < 1$, $p_s > 0.05$. The interaction effect between condition and group was significant, $F(2117) = 4.065$, $P < 0.05$, $\eta_p^2 = 0.065$. The simple effect analysis showed that the N2 amplitude difference between painful and non-painful pictures of the children group was significantly more negative than those of the adolescent and adult groups. The interaction effect between task, condition and group was not significant, $F(2117) = 0.053$, $P > 0.05$.

Fourthly, for ERP component P3, we found the following results. The main effect of task was significant, $F(1117) = 21.305$, $P < 0.001$, $\eta_p^2 = 0.154$. The P3 amplitude in the A-P task was significantly more positive than that in the A-N task. The main effect of condition was significant, $F(1117) = 23.052$, $P < 0.001$, $\eta_p^2 = 0.165$. This was caused by the fact that the P3 amplitude of painful pictures was significantly more positive than that of non-painful pictures. The main effect of group was significant, $F(2117) = 17.258$, $P < 0.001$, $\eta_p^2 = 0.228$. Further post-hoc test revealed that the P3 amplitude of the children group was significantly more positive than those of the adolescent and adult groups, whereas significant difference could not be found between the P3 amplitude of adolescent group and that of adult group. The interaction effect between task and group was not significant, $F(2117) = 1.939$, $P > 0.05$. The interaction effect between condition and group was significant, $F(2117) = 6.462$, $P < 0.05$, $\eta_p^2 = 0.099$. The simple effect analysis showed that the P3 amplitude difference between painful and non-painful pictures of the children group was significantly more positive than those of the adolescent and adult groups. The interaction effect between task and condition was significant, $F(1117) = 12.985$, $P < 0.001$, $\eta_p^2 = 0.100$. Simple effect analysis revealed that in the A-P task, the P3 amplitude of painful pictures was significantly more positive than that of non-painful pictures, whereas in the A-N task, the amplitude difference of P3 component between painful pictures and non-painful pictures did not reach significant level. The interaction effect between

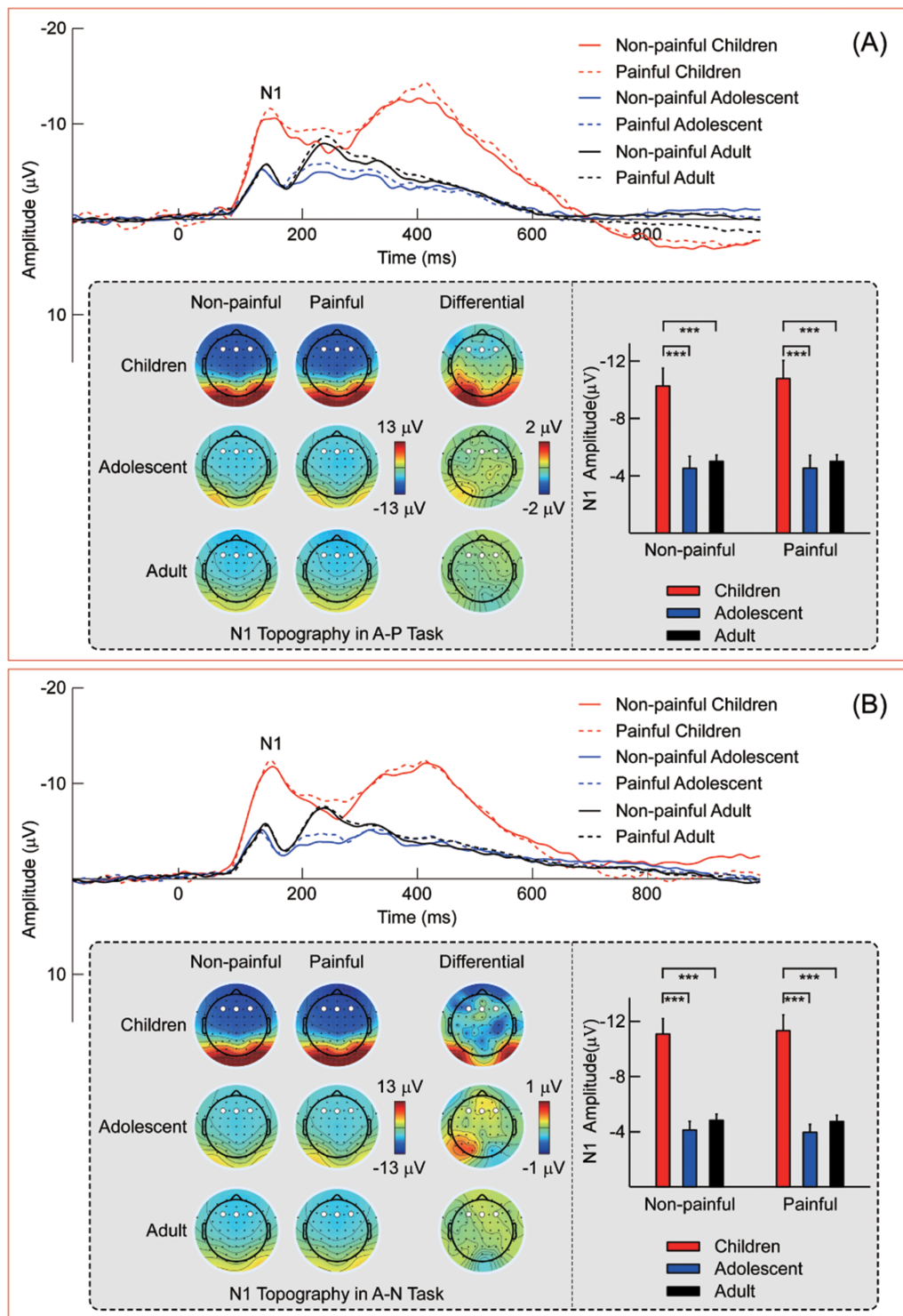


Fig. 4. The ERP waveforms averaged across EOIs of N1 component, topographical maps and the statistical results of N1 component (panel A: A-P task; panel B: A-N task). The white highlighted electrodes are the EOIs (***: $P < 0.001$).

task, condition and group was significant, $F(2117) = 3.138$, $P < 0.05$, $\eta_p^2 = 0.051$. Further analyses showed that in the A-P task, the interaction effect between condition and group was significant. Simple effect analysis showed that in the A-P task, the P3 amplitude difference between painful and non-painful pictures of the children group was significantly more positive than those of the adolescent and adult groups.

Lastly, the statistical test conducted for amplitude of LPC revealed the following results. The main effect of task was significant, $F(1117) = 42.988$, $P < 0.001$, $\eta_p^2 = 0.269$. The LPC amplitude in the A-P task was significantly more positive than that in the A-N task. The main effect of condition was significant, $F(1117) = 36.952$, $P < 0.001$, $\eta_p^2 = 0.240$. This was caused by the fact that the LPC amplitude of painful pictures was significantly more

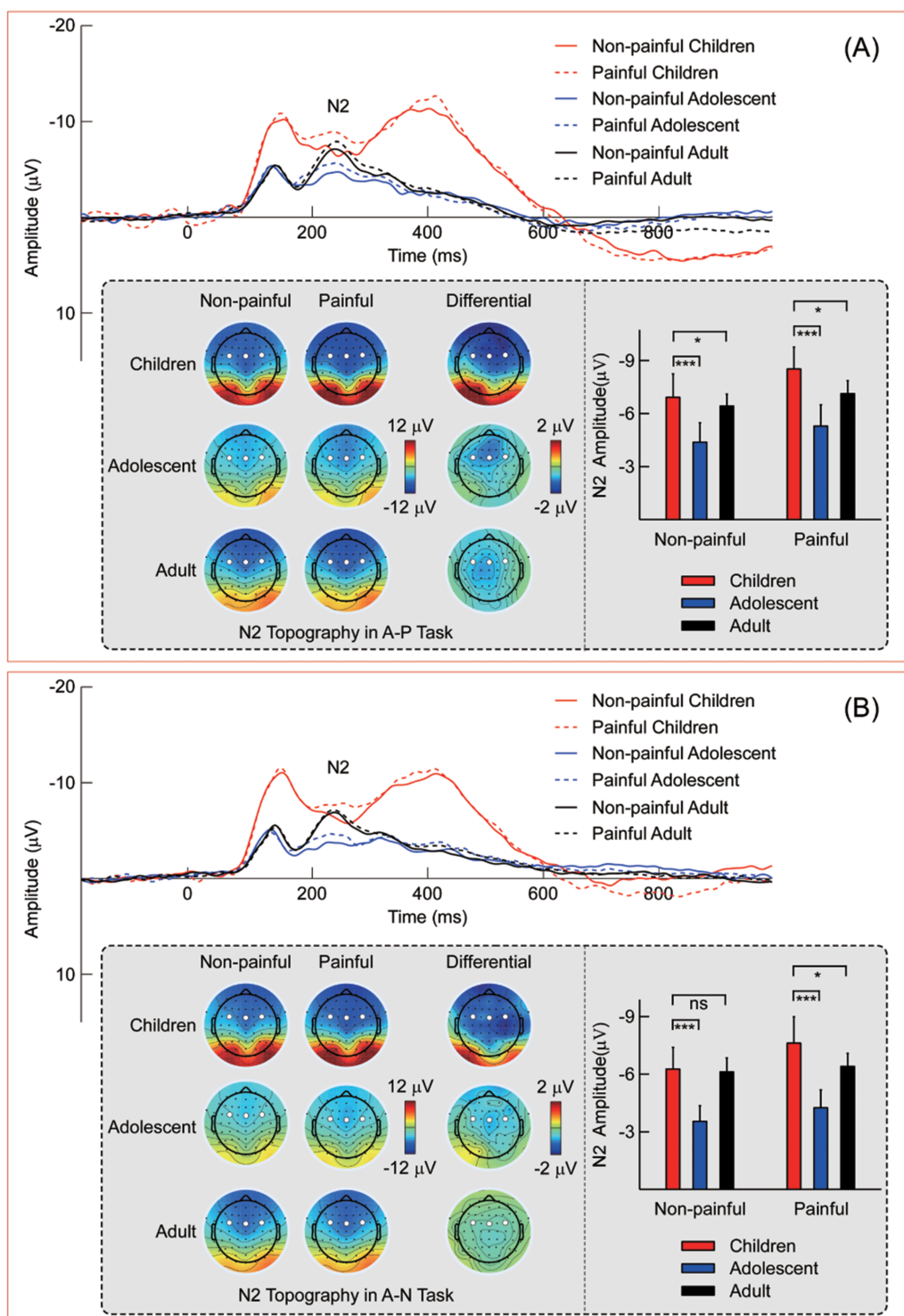


Fig. 5. The ERP waveforms averaged across EOIs of N2 component, topographical maps and the statistical results of N2 component (panel A: A-P task; panel B: A-N task). The white highlighted electrodes are the EOIs (ns: non-significant; *: $P < 0.05$; ***: $P < 0.001$).

positive than that of non-painful pictures. The main effect of group was significant, $F(2,117) = 33.985$, $P < 0.001$, $\eta_p^2 = 0.367$. Further post-hoc test revealed that the LPC amplitude of the children group was significantly more positive than those of the adolescent and adult groups, whereas significant difference could not be found between the LPC amplitude of adolescent group and that of adult group. The interaction effects between task and group and between condition and group were not significant, $F_s < 2$, $p_s > 0.05$.

The interaction effect between task and condition was significant, $F(1,117) = 18.499$, $P < 0.001$, $\eta_p^2 = 0.137$. Simple effect analysis revealed that in the A-P task, the LPC amplitude of painful pictures was significantly more positive than that of non-painful pictures, whereas in the A-N task, the amplitude difference of LPC component between painful pictures and non-painful pictures did not reach significant level. The interaction effect between task, condition and group was not significant, $F(2,117) = 0.176$, $P > 0.05$.

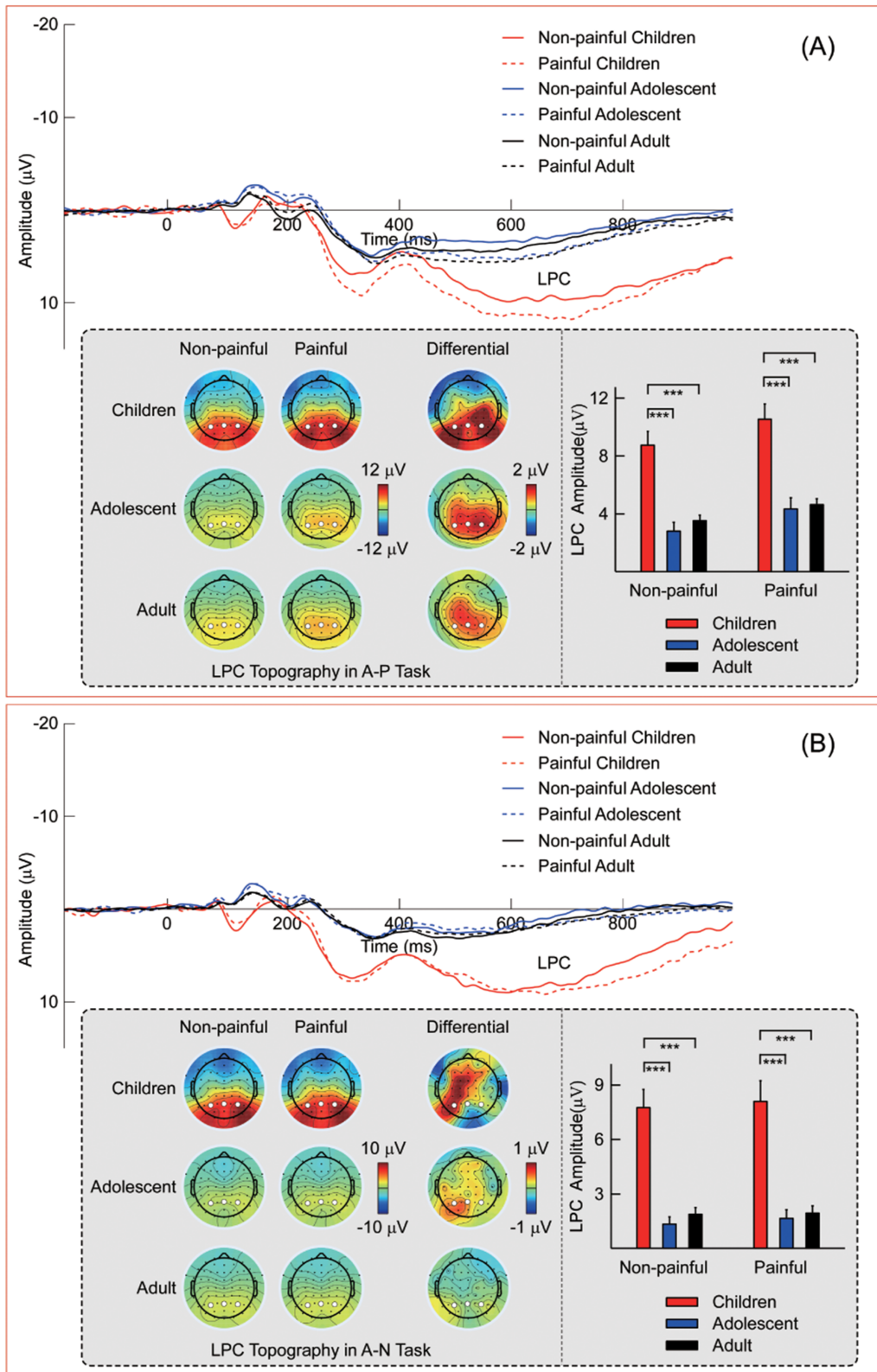


Fig. 6. The ERP waveforms averaged across EOIs of P2/P3 component, topographical maps and the statistical results of P2 and P3 component in the A-P task. The white highlighted electrodes are the EOIs (*: $P < 0.05$; ***: $P < 0.001$).

Discussion

Here, the temporal dynamics of neural processes related to empathy during individual development from childhood through adolescence into adulthood, along with the modulatory effect of

top-down attention on individuals' empathy development, were investigated via two empathy tasks (i.e. the A-P task and the A-N task) and the ERP technique.

Firstly, in the behavioral data analyses, we found that the RT and IES of the children group were significantly longer than those

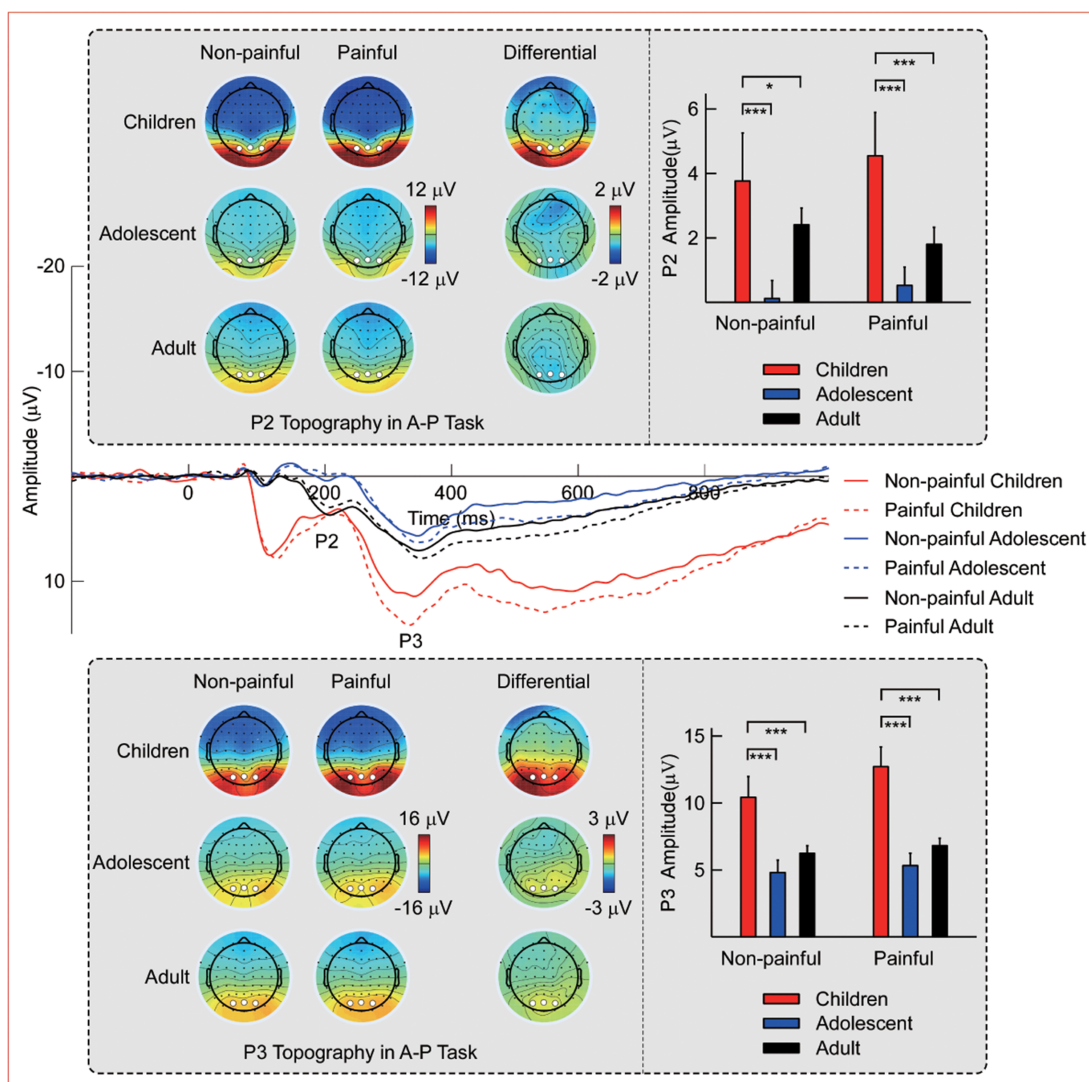


Fig. 7. The ERP waveforms averaged across EOIs of P2/P3 component, topographical maps and the statistical results of P2 and P3 component in the A-N task. The white highlighted electrodes are the EOIs (*: $P < 0.05$; ***: $P < 0.001$).

of the adolescent and adult groups, whereas the ACC of the children group was significantly lower than those of the adolescent and adult groups. As for the main effects of the experimental conditions, compared to the non-painful condition, significantly shorter RT/IES and higher ACC were detected in the painful condition of the A-P task. On the other hand, significantly longer RT/IES and lower ACC were detected in the painful condition of the A-N task.

Secondly, the examination of ERP amplitudes yielded the subsequent findings. Compared to the adolescent and adult groups, the amplitudes of all five ERP components (N1, P2, N2, P3 and LPC) were significantly larger in the children group. As for the main effects of the experimental conditions, compared with the non-painful condition, significantly enlarged N2, P3 and LPC amplitudes were detected in the painful condition of the A-P task, whereas only the N2 amplitude was significantly enlarged in the painful condition of both tasks. Analyzing the differential amplitudes between painful and non-painful conditions revealed that compared with the adolescent and adult groups, the differential amplitudes of P2, N2 and P3 were significantly larger in the children group.

Developmental characteristics of behavioral metrics in pain empathy tasks

Firstly, we found that the RT and IES of the children group were significantly longer than those of the other two groups, whereas the ACC of the children group was significantly lower than that of the other two groups, irrespective of the A-P task and A-N task. The reason behind this phenomenon could be attributed to the fact that the capacity to empathize has not yet attained complete development in these children, thereby leading to potential challenges in accurately assessing whether others are undergoing painful experiences. Another explanation is that compared with the adolescent and adult groups, significantly more attention resources were attracted by the nociceptive cues in these children, which could explain why these group effects could be seen both in the A-P task and the A-N task and is consistent with the ERP results discussed below.

Comparing the behavioral measures of the adolescent group and the adult group, no significant group differences were revealed. This suggests that empathy ability reaches a plateau period when people enter adolescence. The statistical findings of ERP responses were congruent with this observation, as they did

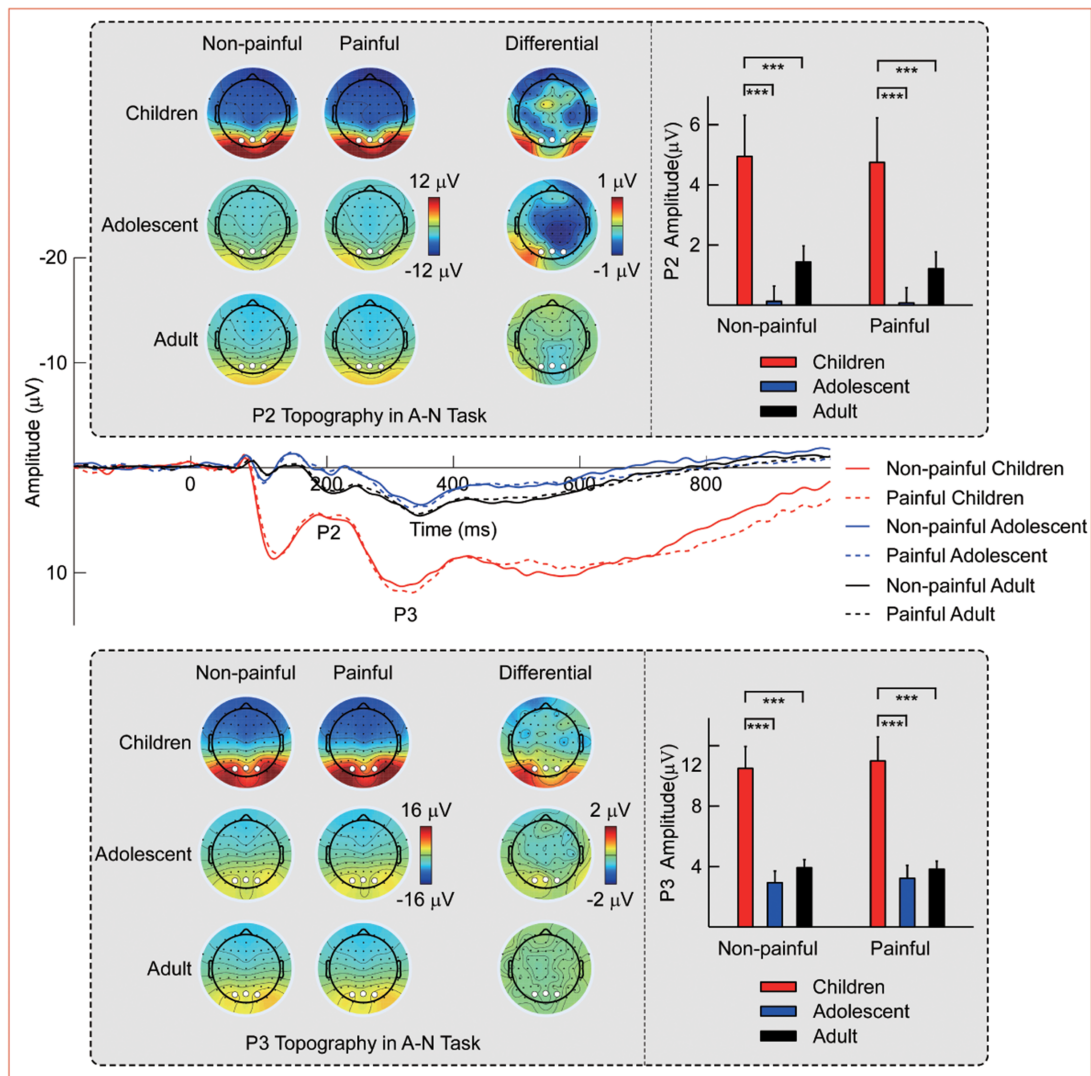


Fig. 8. The ERP waveforms averaged across EOIs of LPC, topographical maps and the statistical results of LPC (panel A: A-P task; panel B: A-N task). The white highlighted electrodes are the EOIs (***: $P < 0.001$).

not identify any significant variances between the adolescent and adult groups.

Secondly, we found that compared to the non-painful condition, significantly shorter RT and higher ACC were detected in the painful condition of the A-P task, whereas significantly longer RT and lower ACC were revealed in the painful condition of the A-N task. The result pattern obtained was in accordance with the investigation conducted by Meng et al. (2019). In the A-P task, participants in all three groups responded significantly more accurately and quickly to painful stimuli than to non-painful stimuli. This indicates a processing bias towards others' pain. In the A-N task, the nociceptive cues within painful pictures attracted participants' attention and interfered with the current task (i.e. number-counting); thus, participants in all three groups responded significantly slower and less accurately to painful stimuli than to non-painful stimuli (Meng et al., 2019).

Developmental characteristics of neural responses in pain empathy tasks

Firstly, we found that compared to the adolescent and adult groups, the amplitudes of all five ERP components were significantly larger in the children group, irrespective of the A-P task and A-N task. This suggests that the neural responses of children when facing second-hand pain-related stimuli were significantly stronger than the other two groups across all mental processing stages. Moreover, this effect is not dependent on top-down attentional allocation and is in line with prior fMRI studies (Decety and Michalska, 2010; Decety et al., 2012). In light of recent research, it has been discovered that individuals of a younger age exhibit heightened activation of specific cortical regions, namely the amygdala, posterior insula and supplementary motor area, when observing others undergoing painful experiences (Decety and Michalska, 2010). A similar pattern could also be seen by Cheng et al. (2014) using the ERP technique, which found that

children displayed greater N2 and LPC amplitudes than adults (Cheng et al., 2014).

Secondly, significantly stronger P3 and LPC responses were evoked by painful pictures than by non-painful pictures in the A-P task. The results are in line with the study conducted by Meng et al. (2019), which demonstrated that images featuring nociceptive cues produced greater P3 and LPC amplitudes compared to images without such cues in an A-P task. The ERP components P3 and LPC, which are largest over the parietal-occipital electrodes, are believed to reflect the late stage of processing others' pain experience (e.g. stimulus evaluation and action preparation) (Coll, 2018; Meng et al., 2020). They are frequently found to be modulated by top-down attention to nociceptive cues. The results for P3 and LPC amplitudes may reflect a greater utilization of cognitive resources in response to painful pictures in the A-P task, which is not observed in the A-N task.

Moreover, we found that compared to non-painful pictures, a significantly larger N2 amplitude was evoked by painful pictures in both the A-P and A-N tasks. The N2 component, maximal at the frontal electrodes, reflects the early processing stage of others' pain information (e.g. automatic emotional contagion and affective sharing process) and could be involuntarily triggered by observing others' pain (Decety et al., 2018). There is a great deal of controversy surrounding the extent to which the amplitude of the N2 component can be modulated by the observation of pain in others. The painful/non-painful effect related to N2 was not observed by Meng et al. (2019), but it was detected by Cheng et al. (2014). Note that, only adult participants were recruited by Meng et al. (2019), whereas both children and adult people participated by Cheng et al. (2014). Thus, the N2 result observed in the present study could be explained by the fact that this 'Painful minus Non-painful' N2 effect may be more discernible in the children group. This assumption was supported by the results by Cheng et al. (2014), which showed that the difference wave between painful and non-painful conditions of N2, indexing empathic arousal, showed an age-related decrease in amplitude.

Thirdly, given that the differential ERP waveforms evoked by painful and non-painful stimuli could denote unique cognitive processes pertaining to nociceptive cues, the differential amplitudes of ERP components could offer further insight into the ways in which individuals across varying age groups perceive nociceptive cues in painful images.

For the two ERP components, P2 and N2, which reflect the early processing stage in empathic processes, we found that the differential amplitude between the painful condition and non-painful condition of the ERP component P2 was significantly larger in the children group for the A-P task. Meanwhile, the differential amplitude of N2 was significantly larger in the children group for both the A-P task and the A-N task. Although both P2 and N2 reflect a relatively early stage in pain empathy, these two components have different scalp distributions and functional significances (Meng et al., 2019). The ERP component P2, which is largest over parietal regions, reflects perceptual processing and is sensitive to automatic attention allocation in pain information processing, whereas the ERP component N2, which is maximal on frontal-central electrodes, is linked to emotional sharing and contagion (Dowman, 2007; Cui et al., 2016). Thus, the above results related to P2 and N2 suggest that top-down attention allocations (i.e. A-P task and A-N task) could modulate specific mental operations in the early processing stage of others' pain. Moreover, these results reflect that automatic attention allocation and emotional contagion are more evident in human childhood.

In the other aspect, the differential amplitudes between painful condition and non-painful condition of ERP component P3 were significantly larger in children group for the A-P task, which may reflect the fact that these children may have difficulty in judging the others within painful context. This is in line with the behavioral results in the A-P task.

The behavioral and neural results regarding the children's group, especially those in the A-N task, could also be explained from the perspective of a broader cognitive control framework. In visual spatial attention, adults are not immune to distraction by salient-but-irrelevant stimuli, but they can exert top-down control in order to minimize this involuntary attention capture. A recent study showed that children are, in fact, more vulnerable to capture by irrelevant stimuli than adults, even after accounting for children's overall cognitive slowing (Gaspelin et al., 2015). This could explain the significantly worse behavioral performance and higher ERP component amplitudes in the children's group.

Limitations of the current study

The current study provided insight into the temporal dynamics of electrocortical processes in pain empathy across individual neurodevelopment stages, spanning from childhood to adolescence and into adulthood. However, the study has a limitation to consider. The participants were divided into three age groups, which may have overlooked the potential for measuring the correlation between the amplitude of ERP components in pain empathy and age more continuously. This oversight could have provided more insight into the specific timing of pain empathy development.

Conclusion

In the current study, we aimed to reveal the developmental characteristics of behavioral and electroencephalographic responses related to empathetic processes, along with the effects of top-down attention and task demands. To achieve this, we recruited three cohorts of participants: a children's group, an adolescent group and an adult group. Each group conducted the A-P task and the A-N task, which directed participants' attention toward and away from potential nociceptive cues, respectively. From the behavioral data analyses, we found that compared to the adolescent and adult groups, the children group responded significantly worse, along with significantly stronger neural responses both in the A-P task and the A-N task. Significantly greater N2, P3 and LPC amplitudes were detected in the painful condition. Moreover, the differential amplitudes between painful and non-painful conditions of P2 and P3 were significantly larger in the children group for the A-P task, while the differential amplitude of N2 was significantly larger in the children group for both the A-P task and A-N task. This P3 differential amplitude could only be modulated by age in the A-P task. Furthermore, no significant group differences were revealed between the adolescent group and adult group, either in behavioral and ERP measures. These results suggest that the capacity to empathize has not yet attained complete development in these children. Significantly more attention resources were involuntarily attracted by the nociceptive cues in these children, which could also reflect the immaturity of empathy ability in these children.

Author contributions

Xiangci Wu (Conceptualization, Methodology, Formal analysis, Writing—original draft), Huibin Jia (Conceptualization, Formal analysis, Writing—original draft), Kaibin Zhao (Formal analysis),

Enguo Wang (Supervision, Funding acquisition, Writing—review & editing) and Yongxin Li (Supervision).

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Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

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