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Maturational changes in the thermoalgesic system in humans from childhood to adulthood revealed by CO_2 laser evoked brain potentials following cutaneous heat stimuli

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Abstract

Possible maturational changes in the thermoalgesic system were studied by reaction times (RT) and late (Adelta-fibre) laser evoked potentials (LEPs) following CO_2 laser heat stimulation of the hand in healthy children ($n = 12$) and young adults ($n = 12$). In children (10 ± 2 years) LEPs presented a negative-positive complex with maximum amplitude (peak-to-peak 71 ± 35 μV) at the vertex and latencies of 248 ± 82 and 433 ± 104 ms, respectively. As compared to adults (24 ± 3 years), children had a significant increased peak-to-peak amplitude (+25.7μV; $P = 0.03$) although no difference in latencies and topography. Median RT (710 ms) was also significantly increased (+312 ms; $P < 0.005$) in children. A decrease in RT and late LEP amplitude from childhood to adulthood may reflect aspects of maturation in sensory processing of the thermoalgesic system.

Keywords: Children; CO_2 laser; Nociception; Laser evoked potentials; Reaction time; Adelta-fibres

Visual, auditory and somatosensory (with electrical stimulation) evoked brain potentials have revealed the existence of processes of cortical maturation from childhood to adulthood [2,3,10]. In general, it was found that most components were of larger amplitude, longer latency and larger variance in children than in adults [3]. The question then arose concerning the existence of similar processes of maturation in the thermoalgesic system. More specifically, do laser evoked brain potentials (LEPs) reveal similar changes from childhood to adulthood?

The laser heat stimulator is really thought to be appropriate for experimental studies of the thermoalgesic system [6,8]. Indeed, thanks to long wavelength radiation (10.6 μm), low penetration (about 50 μm) and high absorptance (99.7%) it can selectively activate the free nerve endings of Adelta- and C-fibres located at the dermo-epidermal junction of the skin [4]. Its high radiation power produces very fast heat ramps [18] allowing better synchronization of the activation of nociceptors which makes the stimulator suitable for recording time locked events such as LEPs and reaction times (RT). Up to now, studies using laser stimulation were mainly focussed on the properties of cutaneous Adelta-fibre afferents and related brain evoked potentials called late LEPs in adults [6,12,14] and no recordings have been made in children.

Twelve healthy children (nine males and three females) volunteered for the present experiments. Their ages ranged from 7 to 13 years (mean ± SD 10 ± 2 years) and their height ranged from 122 to 156 cm (142 ± 10.2 cm). Twelve healthy young adults (nine males and three females) also took part in these experiments. Their ages ranged from 20 to 28 years (24 ± 3 years) and their height from 162 to 192 cm (176 ± 9.1 cm). After presentation of the aim of the study, all volunteers and parents of children gave informed consent for participation following the rules of the Ethics Committee of the University Catholique de Louvain Faculty of Medicine. Subjects were comfortably seated in a chair with their forearms resting on a table. The temperature of the room was kept constant (between 22 and 24°C).

A CO_2 laser was used as a heat stimulator. To localize the stimulation site, a visible low power (5 mW) helium-neon laser was coaxial to the infrared beam. For security reasons, subjects wore protective goggles. To avoid any acoustic interference during stimulation, subjects also wore headphones (Ultramufit, Racal Safety, UK) fed with white noise (60 dB). They nevertheless could perceive a loud sound within the spectral band of the human voice. A warn-

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ing signal was given before each stimulation with a foreperiod varying randomly between 1 and 3 s. Each experimental session started with the determination of the absolute detection threshold (method of ascending limits), i.e. the lowest stimulus intensity detected with a probability of 0.5. With a beam diameter of 1 cm and a stimulus duration of 50 ms, it was 1.1 ± 0.41 and 1.5 ± 0.55 mJ/mm^2 for children and young adults, respectively. A Mann–Whitney test showed no significant difference for the absolute detection threshold between children and young adults ($P = 0.09$). Then, 40 laser stimuli evoking a pinprick sensation (5.8 mJ/mm^2) were applied at random time intervals (25 ± 5 s) to the dorsum of the left hand (between the first and second metacarpal bones). Receptor fatigue or sensitization was avoided by slightly moving the laser beam (within a surface area of 2 × 2 cm) between each stimulus. The mean distance (±SD) between the stimulation site and the *processus spinosus* of C7 was 69 ± 5.7 cm for children and 86 ± 7.6 cm for young adults. The difference in the peripheral conduction distance was statistically significant ($P < 0.001$). The skin temperature of the stimulation site was measured (Tempett®, Senselab, Sweden) before (32.2 ± 1.4°C) and after (32.4 ± 1.2°C) the experimental session.

RT were measured by instructing the subjects to press a button on a joystick as soon as she/he perceived any type of sensation at the stimulation site. All subjects performed this task with the right hand.

Evoked potentials were recorded from seven scalp electrodes (impedance held below 5 kΩ) with linked earlobes (A1/A2 +) as reference. Electrode positions, based on the international 10–20 system, were at frontal, central and parietal midline positions (Fz, Cz, Pz), at central positions (C3 and C4) as well as at temporal positions (T3 and T4). In addition, electrooculogram (EOG) of the right eye was recorded with disposable Ag-AgCl surface electrodes (Medi Trace, Graphics Control, Canada).

Evoked potentials, EOG, RT and laser output signals were recorded on a PLEEG machine (Walter Graphtec, Germany). Signals were filtered (low-pass 75 Hz) and digitized at 167 cps with a 10-bit resolution. Data were stored on disk and analyzed off-line with the NeuroScan software V3.0. The time window for analysis was −500 ms to 2566 ms (512 data points) according to stimulus onset. All trials containing artefacts were rejected from subsequent analysis after visual inspection. Artefact-free trials were time averaged and corrected for baseline offset using the pre-stimulus interval of 500 ms for each channel. LEP components were then described by the amplitude of major deflections in the waveforms in relation to the zero line and by peak latency in relation to stimulus onset. The significance of differences between evoked responses to children and young adults was assessed by means of a *t*-test or a Mann–Whitney test when the normality test or equal variance test failed. In addition, to assess differences in scalp distributions among children and young adults, the amplitude of LEP components was re-analyzed after the data were normalized by vector length as proposed by McCarthy and Wood (1985) [16]. After this vector normalization, differences in scalp distributions were assessed by a two-way repeated measures ANOVA.

Frequency distributions of all RT for children and young adults, shown in Fig. 1, were right skewed. Medians and inter-quartile ranges for all perceived stimuli with a RT value were 710 ms (477 ms) and 398 ms (240 ms) for children and young adults, respectively. There was a statistical difference between children and young adults for median RT ($P = 0.0047$). Notice that RT values obtained for young adults are similar to those obtained from earlier experiments with adults [18] and reported by other investigators [5,7].

After stimulation of the dorsum of the hand, the most prominent aspect in the LEPs waveform consisted of a negative-positive complex. For children, the negative component had a peak latency of 248 ± 82 ms and an average peak amplitude of −12 ± 12.9 μV at Cz. It was followed at 433 ± 104 ms by a large positive component of 59 ± 29.7 μV at Cz. The peak-to-peak amplitude of the negative-positive complex was 71 ± 34.8 μV in children. As shown in Fig. 1, similar LEP waveforms were recorded for young adults. The negative component had a peak latency of 245 ± 55 ms with an average amplitude of −9 ± 10.8 μV at Cz. It was followed by a positive component at 382 ± 83 ms with an amplitude of 36 ± 18.2 μV at Cz. The peak-to-peak amplitude of the negative-positive complex was 45 ± 21.5 μV in adults. There were no statistical differences

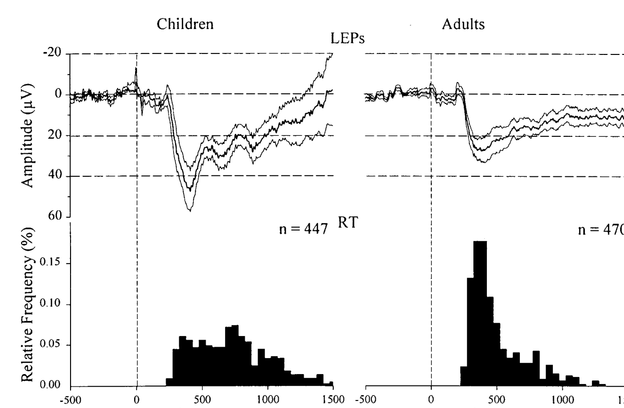

Fig. 1. Grand averages (mean ± SE, thick and thin traces, respectively) of LEPs at electrode Cz (upper) and relative frequency distribution of RT (lower) elicited by CO_2 laser stimuli (duration 50 ms; energy density 5.8 mJ/mm^2; beam diameter 10 mm) applied to the dorsum of the left hand in 12 healthy children (left) and in 12 healthy young adults (right). The vertical dotted line indicates the time point of the laser stimulation. In upper panels, negative values are plotted upwards. Notice that the difference in peak-to-peak amplitude of LEPs between children and young adults was statistically significant ($P < 0.05$). The total number of RT is presented in the right upper corner of panels. Notice the larger distribution of RT for children than for young adults.

between children and young adults either for latencies of the negative ($P = 0.62$) or for latencies of the positive ($P = 0.20$) component. In addition, there were no significant correlations between RT values and LEP component latencies for both groups. The difference in amplitude of the negative component at Cz between both age groups was also not significant ($P = 0.52$). In contrast, there was a statistically significant difference between children and young adults for the amplitude of the positive component at Cz ($P = 0.03$). Study of the scalp distribution showed that this major component, i.e. the positive component, extended over all recorded electrodes and had its largest amplitude at the vertex in 9/12 children and 8/12 young adults.

Differences in scalp distributions of negative and positive components between children and young adults were assessed after vector normalization by a two-way repeated measures ANOVA. There was no statistically significant interaction between electrodes (C3, C4, T3, T4, Fz, Cz and Pz) and condition (children and young adults groups) either for the negative component ($P = 0.973$) or for the positive component ($P = 0.812$).

The aim of these experiments was to reveal possible maturational changes in the thermoalgesic system by studying behavioural responses (RT) and late LEPs (related to Adelta-fibre activation) following CO_2 laser stimulation of the hand in both children and young adults. For the behavioural response, we observed a significant difference in median and inter-quartile range RT values. This was already observed in similar studies with other sensory modalities and should be interpreted on the bases of central effects like maturation of attention, speed of information-processing and decision-making but also by development of motor performance from childhood to adulthood [11,17]. Indeed, the difference in median RT values (i.e. 312 ms) can not be explained solely by a difference in the peripheral conduction distance (arm length) between age groups. Considering a conduction velocity of Adelta-fibres ranging from 20 to 4 m/s [1,13,19] and a difference in the peripheral conduction distance of 0.17 m between groups, one can estimate that for young adults, RT should be increased on average by only 8–40 ms as compared to children. For similar reasons, the difference in RT values between children and young adults was not reflected in peak latencies of late LEP components. Indeed, no difference in peak latencies was observed between both groups. The expected small increase in latency with growth in arm length has not been observed possibly due to the large intersubject variance of latencies especially for children and the limited number of subjects in each group ($n = 12$). On the other hand, the absence of a difference in latency may translate to the fact that transmission velocity in Adelta-fibres (due to an increase in axonal diameter and myelinization) and perceptual processing speed reach maturity at an earlier stage of development.

The experimental paradigm and recording parameters fulfil the conditions for producing a contingent negative variation (CNV). This CNV was indeed observed (Fig. 1) but was relatively small (on average 6 μV/s) and the parameters of the negative wave were not different between age groups. So, the influence of CNV on late LEP components should presumably be similar for both groups.

The most significant effect of maturation on LEPs was the decrease in peak-to-peak amplitude and more specifically the late positive component amplitude. This was also observed for visual [3], auditory [2] and somatosensory [10] evoked potentials. One direct interpretation is that the amplitude of source activity could be higher with lower head size and thinner skulls. However, changes in amplitude may also indicate changes in synchronization and effectiveness of perceptual networks but as well increasing automation of sensory processing [2]. Furthermore, studies using brain electrical source analysis (for review see Refs. [9,15]) show that the late positive component could be explained by multiple intricate sources (SII-insula, cingulate cortex and anterior middle temporal areas such as the amygdala or hippocampus in the bilateral hemispheres). Thus, further studies using for instance attentional modulation are needed to explore the possible relationship between a decrease in late positive component amplitude and maturation and to unravel the contribution of the different sources.

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