Clinical Neurophysiology Practice 10 (2025) 141–149

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

# Changing characteristics of somatosensory evoked potentials in adolescents

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ARTICLE INFO

*Keywords:*
Somatosensory processing
SEP
Electroencephalogram
Puberty
Primary somatosensory cortex
Sex differences

ABSTRACT

*Objective:* We investigated changing characteristics of somatosensory processing in adolescents, particularly sex differences, by comparing children, young adults, and males and females.
*Methods:* Participants included 26 elementary school children (ESC), 36 adolescents (ADO), and 36 college students (CS). We recorded somatosensory evoked potentials (SEPs) using electrical stimulation of the right median nerve. Peak latencies and amplitudes were measured for P12, N15, P18, and N30 at Fz, and for P12 (P1), N18 (N1), P22 (P2), N27 (N2), P3, N3, P45 (P4), and N60 (N4) at C3′.
*Results:* The P22 (P2) amplitude at C3′ decreased with age. The N15 amplitude at Fz was larger in females across all groups. P3 and N3 occurrence at C3′ decreased with age but remained high in ADO compared to CS. Correlation analysis showed a significant negative correlation between P22 (P2) amplitude at C3′ and age in ADO boys, but not in ADO girls, ESC boys, or ESC girls.
*Conclusions:* Somatosensory processing in ADO is not as mature as in CS, with sex differences between ADO boys and girls.
*Significance:* Our findings may aid understanding of neural activity in children with developmental disorders, supporting sensory-based therapies.

## 1. Introduction

Somatosensory evoked potentials (SEPs) are recorded using electrical stimuli to assess somatosensory processing and reflect neural activity after the stimulation of nerves, such as the median nerve. There are two pathways of somatosensory processing in the human brain: a posterior pathway from Brodmann's area 3b of the primary somatosensory cortex (SI) to areas 1 and 2; and an anterior pathway from area 3b to areas 4, 6, and 8 (Cebolla et al., 2011; Inui et al., 2004). Median nerve stimulation elicits SEP components at centroparietal (P12, N18, P22, N27, P45, N60) and frontal (P12, N15, P18, N30) electrodes (Nakata et al., 2015; Takezawa et al., 2019).

Several previous studies investigated the characteristics of somatosensory cognitive processing in children, focusing on centroparietal electrodes (Boor et al., 1998; Geneva et al., 2002; Taylor and Fagan, 1988; Zanini et al., 2016). Geneva et al. (2002) recorded SEPs in 67 children (0–16 years) and found that P15, N20, and P25 latencies increased with height. The N20/P25 amplitude ratio increased with age, although individual amplitudes showed no age-related changes. Notably, Takezawa et al. (2019) identified a difference in waveforms of children compared with young adults at the centroparietal (C3′) electrode. In SEP waveforms of prepubescent children, components such as P3 and N3, which are not observed in adult waveforms, were noted between the N27 (N2) and P45 (P4) components. N27 mainly reflects neural activity of Brodmann's area 2, while P45 and N60 reflect that of SI and the supplementary motor area (SMA) (Barba et al., 2001, 2008; Inui et al., 2004). The generator mechanisms underlying P3 and N3 in prepubescent children remain unclear; however, neural activities in SI and SMA may be involved. Additionally, the amplitude of the P22 (P2) component was significantly larger in elementary school children compared with adults.

Gray matter volume peaks around age 15 and declines through adolescence, while that of white matter increases into adulthood (Mills et al., 2016; Winkler et al., 2012; Herting et al., 2017). These changes in development of gray and white matter, primarily observed during puberty, are closely related to the physical and hormonal changes during this period. According to a review by Kaczkurkin et al. (2019), while no sex differences in the density of cortical and subcortical gray matter are observed at the age of 8, after adolescence, females tend to have a higher density compared with males.

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https://doi.org/10.1016/j.cnp.2025.03.004
Received 26 November 2024; Received in revised form 26 March 2025; Accepted 29 March 2025
Available online 5 April 2025

Many studies using SEPs in adolescents examined only the characteristics of subcortical components including the brainstem and thalamus or early cortical components (Boor et al., 1998; Geneva et al., 2002; Taylor and Fagan, 1988; Zanini et al., 2016), and no studies recording SEPs considered two pathways demonstrating somatosensory processing. Our previous study demonstrated immature somatosensory neural activity in elementary school children (Takezawa et al., 2019), but it is unclear whether this neural activity reaches adult levels in adolescents. Furthermore, it is not known whether sex differences exist in the nervous system regarding somatosensory processing between adolescent male and female children. Research on the adolescent brain might help to explore the causes of adolescent-specific behavioral and emotional changes and devise mental health interventions and support methods.

This study examined adolescent somatosensory processing changes and sex differences by comparing elementary school children and adults.

## 2. Methods

### 2.1. Participants

Twenty-six elementary school children (ESC; 14 girls and 12 boys), thirty-six adolescents (ADO; 20 girls and 16 boys), and thirty-six college students (CS; 20 females and 16 males) with right-handedness participated in this study. Some of the data in elementary school children have already been published (Takezawa et al., 2019). Mean ages were 10.0 ± 0.2, 14.1 ± 0.3, and 21.0 ± 1.0 years in ESC, ADO, and CS respectively. The mean height of males was 139.8 ± 4.7 cm in ESC, 165.4 ± 8.4 cm in ADO, and 173.0 ± 6.3 cm in CS, while that of females was 139.8 ± 4.6, 157.5 ± 7.0, and 157.9 ± 3.7 cm, respectively. Any ESC with signs of puberty (self- or parent-reported) were excluded. None of the subjects had a history of neurological or psychiatric disorders.

Informed consent was obtained from all participants and children's guardians. The procedures used complied with the Declaration of Helsinki regarding human experimentation. This study was approved by the Ethical Committee of Nara Women's University, Nara City, Japan (approval number: 22–65).

### 2.2. Procedure

In order to record SEPs, the electric stimulus used was a constant current square-wave pulse delivered to the right median nerve using a pair of felt-up electrodes. The stimulus duration was 0.2 ms, and the stimulus intensity was sufficient to produce a slight but definite twitch of the thumb. Participants were asked to stay relaxed and not to pay attention to the stimuli. Approximately two hundred stimuli were applied in total.

### 2.3. EEG recordings and data analysis

EEG was recorded with Ag/AgCl disk electrodes placed on the scalp at Fz, Cz, Pz, and C3′ (C3′ was 2 cm posterior to C3), according to the International 10–20 System. Each scalp electrode was referenced to linked earlobes which were mathematically calculated as an averaged reference. In order to preclude interference noise due to eye movements or blinks exceeding 100 μV, an electrooculogram (EOG) was recorded bipolarly with a pair of electrodes placed 2 cm lateral to the lateral canthus of the right eye and 2 cm above the upper edge of the right orbit and analyzed on-line. We also checked all raw data off-line, and if clear artifacts not exceeding 100 μV (unexplained noise) were recorded, the trials were eliminated from averaging. Impedance was maintained at less than 5 kohm. All EEG signals were collected on a signal processor (Neuropack X1 system, Nihon-Kohden, Tokyo, Japan). For the recording of SEPs, the bandpass filter was 1–1,500 Hz. The analysis time was 100 ms, and the sampling rate was 5,000 Hz. The peak amplitudes and latencies for individual SEP components were obtained using a measuring scale of the Neuropack system with visual inspection. The peaks of all recognizable SEP components were measured. The peak amplitude of each component was identified immediately prior (peak-to-peak). Thus, the amplitude for the first P12 (P1) component was not shown. We focused on Fz and C3′ electrodes, and Cz and Pz electrodes were supplementarily set up based on previous studies. Peak amplitudes at Fz were measured for N15, P18, and N30. Peak amplitudes at C3′ were measured for N18 (N1), P22 (P2), N27 (N2), P3, N3, P45 (P4), and N60 (N4). N18 (N1) at C3′ in children is equivalent to the N20 component in adults, primarily due to the influence of height. Previous studies suggested that differences in somatosensory evoked potential latencies between children and adults are partially attributed to variations in nerve conduction distance, which is affected by body height (Boor et al., 1998; Geneva et al., 2002; Takezawa et al., 2019; Taylor and Fagan, 1988; Zanini et al., 2016). Thus, N18 in children reflects the same neural processing as N20 in adults, adjusted for developmental differences in physiological structure.

### 2.4. Statistical analysis

SEP data on the latency and amplitude for each component were separately subjected to two-way analyses of variance (ANOVA) with Group (ESC, ADO, and CS) and Sex (female and male) as factors. Amplitudes of SEPs at C3′ for N1, P2, N2, P4, and N4, and at Fz for N15, P18, and N30 components were analyzed. Latencies were analyzed similarly for P1, N1, P2, N2, P4, and N4 at C3′, and for P12, N15, P18, and N30 at Fz. Additionally, data on height were submitted to two-way ANOVA with Group and Sex as factors. If the results of Mauchly's test were significant and the assumption of sphericity was violated, Greenhouse-Geisser adjustment was used to correct sphericity by altering the degrees of freedom using a correction coefficient epsilon. When a significant main effect for Group was identified, Bonferroni post-hoc multiple-comparison was employed to identify specific differences. Furthermore, if a significant main effect for Sex was obtained, an unpaired *t*-test was conducted as a post-hoc test.

We also analyzed the bivariate correlation between SEP components and age in months among ESC and ADO, and between SEP components and height among all subjects. This analysis was performed after checking data had a normal distribution using the Kolmogorov-Smirnov test. If a normal distribution was confirmed, Pearson's correlation was calculated. If non-parametric data were found, Spearman's correlation was used. Significance was set at $p < 0.05$.

## 3. Results

### 3.1. Anthropometric data

ANOVAs for height showed a significant main effect of Group ($F(2, 92) = 146.836$, $p < 0.001$, $\eta^2 = 0.761$). The post-hoc test showed that CS were significantly taller than ADO ($p < 0.05$), and ADO and CS were taller than ESC ($p < 0.01$, respectively). A significant main effect of Sex was also observed ($F(1, 92) = 38.029$, $p < 0.001$, $\eta^2 = 0.292$), indicating that males were taller females.

### 3.2. The peak amplitude and latency of SEP at Fz

Figs. 1 and 2 show grand-averaged SEP waveforms across all participants for each group at Fz and C3′ electrodes.

ANOVAs for the peak amplitude showed a significant main effect of Sex on N15 ($F(1, 90) = 7.988$, $p < 0.01$, $\eta^2 = 0.82$), indicating that the peak amplitude was larger in females than males. No significant difference in peak amplitudes were observed in P18 and N30 (Fig. 3).

ANOVAs for the peak latency showed a significant main effect of Group on P12 ($F(2, 90) = 13.642$, $p < 0.001$, $\eta^2 = 0.233$). The post-hoc test showed that the latency was significantly shorter in ESC than in ADO and CS ($p < 0.01$, respectively). A significant main effect of Sex was also

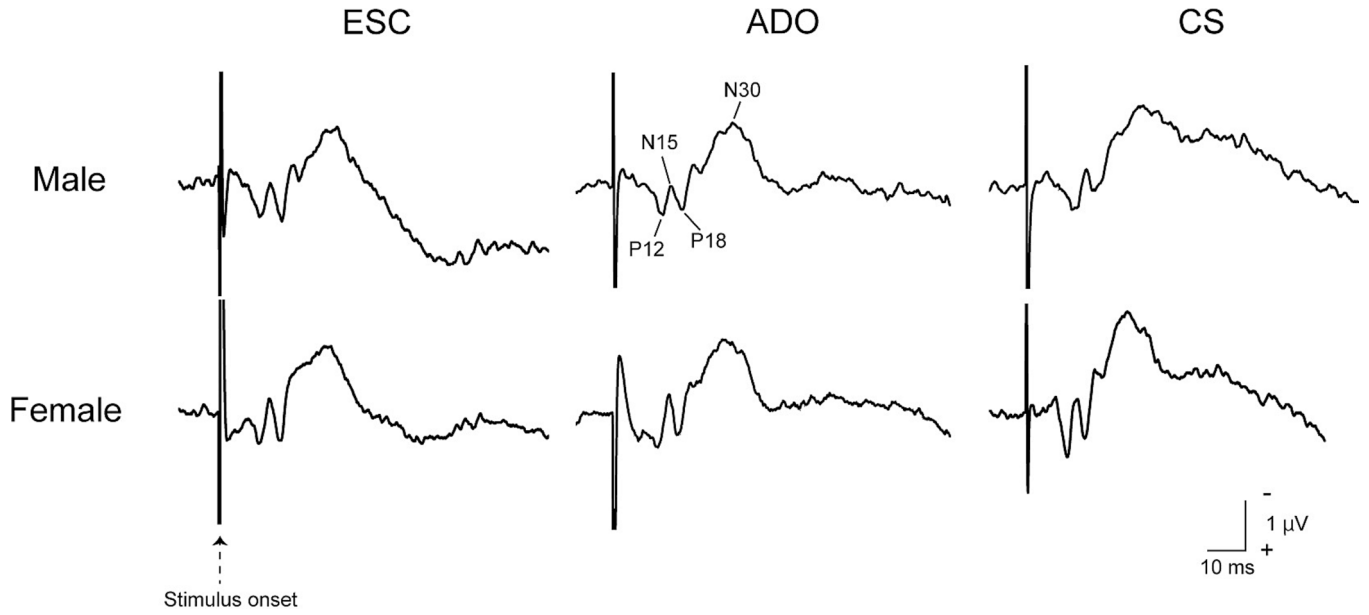


**Fig. 1.** Grand-averaged SEP waveforms at Fz across all participants in each group ESC = elementary school children; ADO = adolescents; CS = college students.

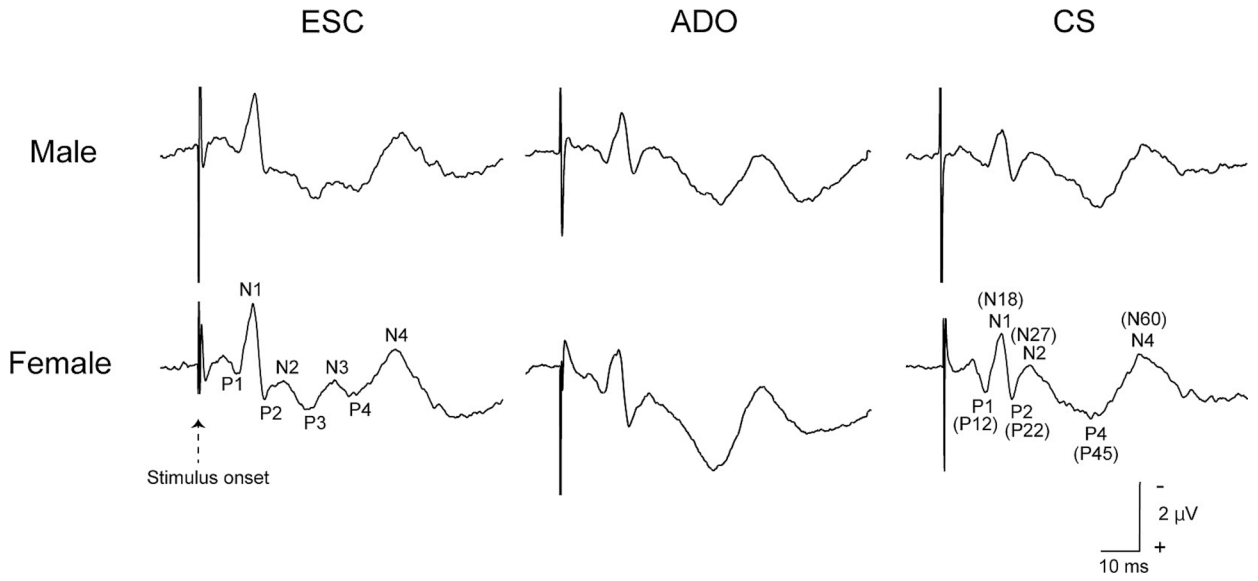


**Fig. 2.** Grand-averaged SEP waveforms at C3′ across all participants in each group ESC = elementary school children; ADO = adolescents; CS = college students.

observed ($F(1, 90) = 14.188$, $p < 0.001$, $\eta^2 = 0.136$), indicating that the peak latency on P12 was shorter in females than males.

ANOVAs for N15 showed a significant main effect of Group ($F(2, 90) = 27.268$, $p < 0.001$, $\eta^2 = 0.377$). The post-hoc test showed that the latency was significantly shorter in ESC than in ADO and CE ($p < 0.001$, respectively). A significant main effect of Sex was also observed, indicating that the peak latency on N15 was shorter in females than males ($F(1, 90) = 15.018$, $p < 0.001$, $\eta^2 = 0.143$).

ANOVAs for P18 showed a significant main effect of Group ($F(2, 90) = 16.935$, $p < 0.001$, $\eta^2 = 0.273$). The post-hoc test showed that the latency was significantly shorter in ESC than in ADO and CS ($p < 0.001$, respectively). A significant main effect of Sex was also observed, indicating that the peak latency on P18 was shorter in females than males ($F(1, 90) = 15.125$, $p < 0.001$, $\eta^2 = 0.144$). No significant difference in the peak latency was observed in N30 at Fz (Table 1).

### 3.3. The peak amplitude and latency of SEP at C3′

ANOVAs for the peak amplitude showed a significant main effect of Group on P22 (P2) ($F(2, 92) = 4.514$, $p < 0.05$, $\eta^2 = 0.089$). The post-hoc test showed that the amplitude was significantly larger in ESC than CS ($p < 0.05$). ANOVAs for the peak amplitude on P45 (P4) showed a significant main effect of Group ($F(2, 92) = 5.633$, $p < 0.01$, $\eta^2 = 0.109$). The post-hoc test showed that the amplitude was larger in ADO than ESC ($p < 0.01$). No significant differences in the peak amplitudes were observed in N18 (N1), N27 (N2), or N60 (N4) at C3′ (Fig. 3).

ANOVAs for the peak latency on P12 (P1) showed a significant main effect of Group ($F(2, 92) = 16.549$, $p < 0.001$, $\eta^2 = 0.265$), and Sex ($F(1, 92) = 16.529$, $p < 0.01$, $\eta^2 = 0.105$), and Group-Sex interaction ($F(2, 92) = 3.170$, $p < 0.05$, $\eta^2 = 0.064$). The post-hoc test for male subjects showed that the latency was significantly shorter in ESC than in ADO and CS ($p < 0.05$, $p < 0.001$, respectively), and female subjects also showed a shorter latency in ESC ($p < 0.05$, respectively). The post-hoc *t*-

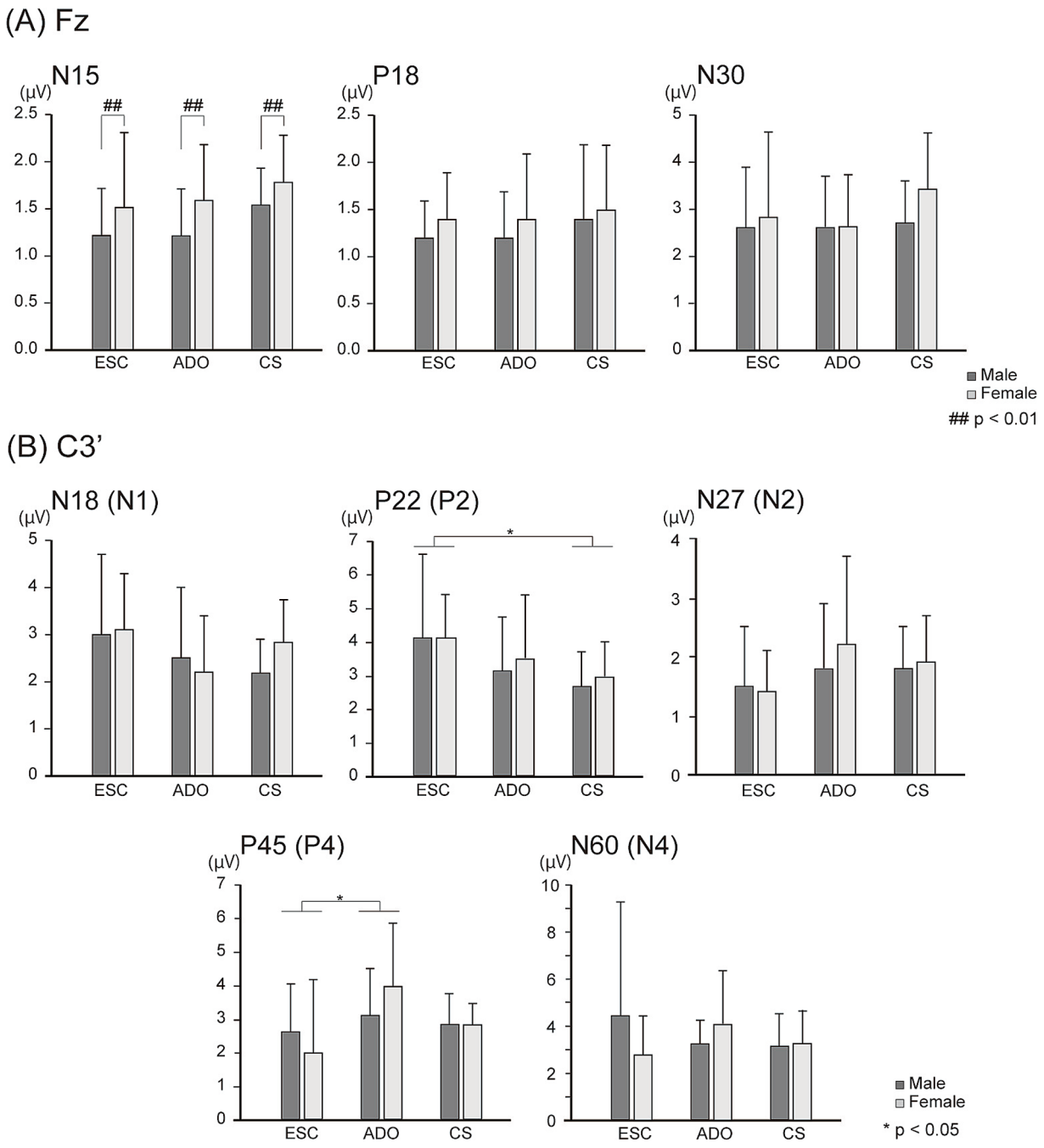


**Fig. 3.** Mean values of each component in SEP amplitudes (A) at Fz and (B) at C3′. ESC = elementary school children; ADO = adolescents; CS = college students. Vertical lines indicate SDs.

test for ESC and ADO showed no significant difference between boys and girls. The *t*-test for CS showed a significant difference between males and females ($p < 0.001$), indicating that the peak latency on P12 (P1) was shorter in females than males.

ANOVAs for the peak latency on N18 (N1) showed a significant main effect of Group ($F(2, 92) = 28.189$, $p < 0.001$, $\eta^2 = 0.380$), and Sex ($F(1, 92) = 25.790$, $p < 0.001$, $\eta^2 = 0.219$), and Group-Sex interaction ($F(2, 92) = 5.068$, $p < 0.01$, $\eta^2 = 0.099$). The post-hoc test for male subjects showed that the latency was significantly shorter in ESC than in ADO and CS ($p < 0.001$, respectively), and female subjects also showed a shorter latency in ESC ($p < 0.001$, $p < 0.05$, respectively). The post-hoc *t*-test for ESC showed no significant difference between boys and girls. The *t*-test for ESC and CS showed a significant difference in sex ($p < 0.001$, respectively), indicating that the peak latency on P12 (P1) was shorter in females than males.

ANOVAs for the peak latency on P22 (P2) showed a significant main effect of Sex ($F(1, 92) = 18.288$, $p < 0.001$, $\eta^2 = 0.166$), indicating that the peak latency on P22 (P2) was shorter in females than males. ANOVAs for the peak latency on N27 (N2) showed a significant main effect of Sex ($F(1, 92) = 7.486$, $p < 0.01$, $\eta^2 = 0.075$), indicating that the peak latency on N27 (N2) was shorter in females than males. No significant difference in the peak latency was observed in P45 (P4) or N60 (N4) (Table 1).

### 3.4. The characteristics of P3 and N3 components at C3′

Fig. 4A shows grand-averaged SEP waveforms in male and female ADO groups including P3 and N3 components, and Fig. 4B shows grand-

**Table 1**
Mean values for peak latencies of each SEP component.

| | | | | | Main effect of ANOVA | |
|---|---|---|---|---|---|---|
| (ms) | Sex | ESC | ADO | CS | Group | Sex |
| Fz | | | | | | |
| P12 | M | 11.7 (1.2) # | 12.9 (0.9) *# | 13.0 (1.0) *# | < 0.001 | < 0.001 |
| | F | 11.3 (0.6) | 12.0 (0.8) * | 12.2 (0.5) * | | |
| N15 | M | 14.2 (0.9) # | 15.9 (1.3) *# | 16.0 (1.0) *# | < 0.001 | < 0.001 |
| | F | 13.9 (0.5) | 15.1 (0.4) * | 15.1 (0.8) * | | |
| P18 | M | 17.1 (1.1) # | 18.4 (1.2) *# | 18.8 (1.1) *# | < 0.001 | < 0.001 |
| | F | 16.6 (0.5) | 17.7 (1.0) * | 17.7 (0.8) * | | |
| N30 | M | 29.9 (2.0) | 30.9 (3.0) | 30.9 (1.8) | 0.158 | 0.178 |
| | F | 29.2 (1.6) | 30.3 (2.2) | 30.2 (2.6) | | |
| C3′ | | | | | | |
| P12 (P1) | M | 11.8 (1.1) | 13.1 (1.1) * | 13.8 (1.2) * | < 0.001 | < 0.01 |
| | F | 11.6 (1.1) | 12.7 (0.9) * | 12.4 (0.6) * | | |
| N18 (N1) | M | 16.3 (0.8) | 18.5 (1.0) * | 18.1 (1.0) * | < 0.001 | < 0.001 |
| | F | 16.2 (0.6) | 17.0 (0.8) * | 17.2 (0.7) * | | |
| P22 (P2) | M | 21.3 (2.0) # | 22.0 (1.7) # | 21.7 (1.5) # | 0.371 | < 0.001 |
| | F | 20.3 (1.5) | 20.6 (1.4) | 20.0 (0.8) | | |
| N27 (N2) | M | 26.8 (3.7) # | 26.3 (2.0) # | 27.0 (2.7) # | 0.443 | < 0.01 |
| | F | 24.0 (2.1) | 26.0 (2.7) | 25.5 (2.0) | | |
| P45 (P4) | M | 45.6 (6.7) | 44.8 (6.0) | 44.9 (3.7) | 0.363 | 0.445 |
| | F | 45.7 (5.7) | 44.6 (3.8) | 42.7 (4.1) | | |
| N60 (N4) | M | 59.5 (4.6) | 58.8 (2.6) | 60.6 (2.6) | 0.453 | 0.065 |
| | F | 58.3 (4.5) | 58.3 (3.1) | 58.5 (2.7) | | |

Data are expressed as the mean (SD). ANOVAs showed Group-Sex interactions for P12 and N18 components at C3′. Significant differences are shown as factors of Group (vs. prepubescent children): * $p < 0.05$; Sex (male vs. female): # $p < 0.05$. M = male; F = female. ESC = elementary school children; ADO = adolescents; CS = college students.

averaged SEP waveforms in male and female ADO groups without these components.

Table 2 shows the occurrence rates of P3 and N3 components observed between N27 (N2) and P45 (P4) components at C3′ in each age group. The occurrence rate was 75.0 % in ESC boys, 85.7 % in ESC girls, 43.8 % in ADO boys, 30.0 % in ADO girls, 18.8 % in CS males, and 0.0 % in CS females.

### 3.5. The relationship between SEP components and age in months

Mean ages were 124.9 ± 3.8, and 175.4 ± 3.3 months in ESC and ADO respectively. Fig. 5 shows correlation analysis between the amplitude in P22 (P2) at C3′ and age in months for ESC and ADO individuals. A significant negative correlation was observed in ADO boys ($r = -0.639$, $p = 0.008$), indicating that the amplitude P22 (P2) decreased with increasing age in months. In contrast, no significant correlations were observed between them among ESC and ADO girls.

### 3.6. The relationship between SEP components and height

Table 3 shows correlation analysis between SEP components and height. Significant positive correlations were observed in SEP latency of P12 ($r = 0.596$, $p < 0.001$), N15 ($r = 0.664$, $p < 0.001$), P18 ($r = 0.636$, $p < 0.001$), and N30 ($r = 0.271$, $p < 0.01$) at Fz, and P12 (P1) ($r = 0.647$, $p < 0.001$), N18 (N1) ($r = 0.690$, $p < 0.001$), P22 (P2) ($r = 0.359$, $p < 0.001$), and N27 (N2) ($r = 0.215$, $p < 0.05$) at C3′. These results indicate that taller subjects had a longer SEP latency. Significant negative correlations were observed in SEP amplitude of N18 (N1) ($r = -0.212$, $p < 0.05$) and P22 (P2) ($r = -0.215$, $p < 0.05$) at C3′, indicating that these amplitudes decreased with increasing height. On the other hand, significant positive correlations were observed in N27 (N2) ($r = 0.224$, $p < 0.05$) and P45 (P4) ($r = 0.255$, $p < 0.05$) at C3′, indicating that taller subjects had a larger amplitude.

### 3.7. Covariate analysis of P22 (P2) amplitude

To further investigate age-related changes in the P22 (P2) amplitude, we conducted an analysis of covariance (ANCOVA) with height as a covariate. The analysis showed no significant main effect of height nor interactions on the P22 (P2) amplitude.

## 4. Discussion

We investigated the changing characteristics of somatosensory processing across puberty using SEPs, by comparing those among prepubescent children and adults, and examined sex differences in SEP waveforms across three age groups.

The latencies of P12, N15, and P18 at Fz, as well as P12 (P1) and N18 (N1) at C3′ were short in females and the ESC group, while P22 (P2) and N27 (N2) at C3′ were shorter in females than males (Table 1). These results would be related to anthropometric data. That is, males were significantly taller than females, and height increased with age. Previous studies on SEPs showed positive correlations between height or arm length and latencies (Boor et al., 1998; Geneva et al., 2002; Takezawa et al., 2019; Taylor and Fagan, 1988; Zanini et al., 2016), being consistent with the results of the present study. As mentioned in Introduction, anterior and posterior pathways from Brodmann's area 3b exist in somatosensory processing. Neural activities in an anterior pathway, generated from the prefrontal, premotor, and primary motor cortices, can be recorded at Fz electrode (Cebolla et al., 2011; Urushihara et al., 2006). A posterior pathway included neural activities from Brodmann's area 3b of SI to areas 1 and 2 (Inui et al., 2004; Takezawa et al., 2019). P12 and N15 are generated from higher segments of the cervical cord, and at or near the foramen magnum (Cruccu et al., 2008; Restuccia et al., 1995). In the present study, since significant differences in SEP latencies were observed at P12, N15, and P18 at Fz, and P12 (P1), N18 (N1), P22 (P2), and N27 (N2) at C3′, the height may influence the subcortical and early cortical components. These results are consistent with part of the findings reported by Geneva et al. (2002), who recorded SEPs in children and reported that the latencies of P15, N20, and P25 delayed with increasing height. Thus, middle and late SEP components including P45 (P4) and N60 (N4) at C3′ were not affected by the height. This might be associated with the latency jitter among subjects. Indeed, in Table 1, the standard deviations (SDs) were clearly larger in N30 at Fz and P45 (P4) and N60 (N4) at C3′ than in other components, suggesting that individual differences were marked in middle and late SEP components. These data were also supported by correlation analysis between SEP components and height (Table 3).

ANOVA for the amplitude of P22 (P2) at C3′ showed a significant main effect of Group, indicating that the amplitude decreased with increasing age (Fig. 3). N18 is generated from area 3b of the SI (Allison et al., 1991), whereas P22 (P2) is generated from areas 1 and 4 (Inui et al., 2004). Anatomical studies demonstrated that area 1 received direct thalamocortical connections from the ventral lateral nucleus and area 3b (Jones, 1986; Jones et al., 1978). Alternatively, area 3b mainly received connections from the ventral lateral nucleus. Takezawa et al. (2019) compared the characteristics of SEPs between elementary school children and young female adults, and reported that the amplitude of P22 (P2) at C3′ was significantly larger in children than adults. They mentioned hyper-excitability/responsiveness of neural activity on somatosensory processing in children. Our data suggest that this change reflects maturation of the cerebral cortex, especially at areas 1 and 4, and a reduction in the hyper-excitability/responsiveness. Further analysis using ANCOVA with height as a covariate revealed no significant

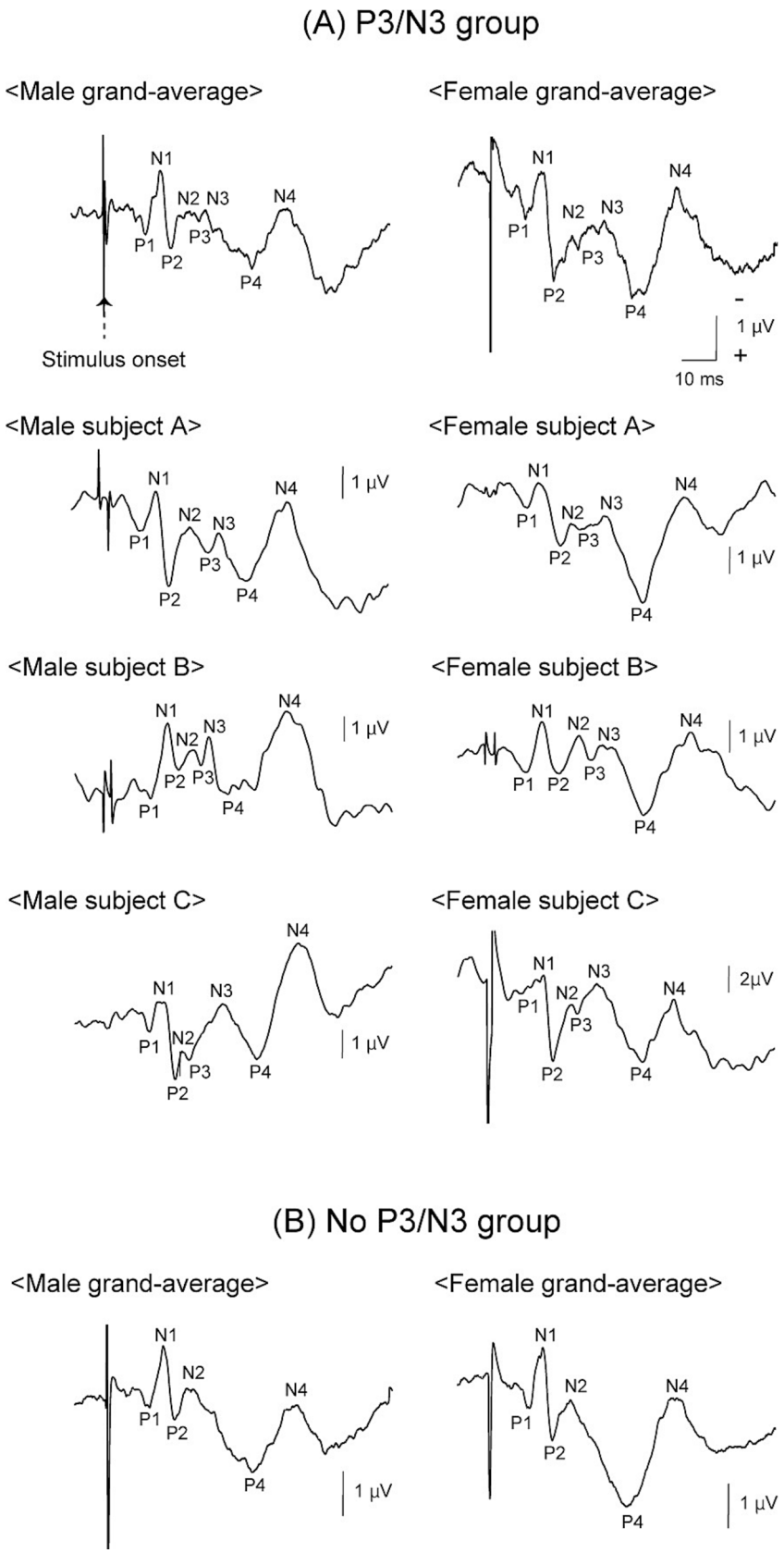


**Fig. 4.** (A) Grand-averaged SEP waveforms in male and female ADO groups including P3 and N3 components. (Lower figures) Individual waveforms in six representative subjects are shown. (B) Grand-averaged SEP waveforms in male and female ADO groups without these components.

**Table 2**
Occurrence rates of P3 and N3 components in each age group.

| | Male | Female |
|---|---|---|
| ESC | 75.0 % | 85.7 % |
| ADO | 43.8 % | 30.0 % |
| CS | 18.8 % | 0 % |

ESC = elementary school children; ADO = adolescents; CS = college students.

main effect of height nor its interactions on the P22 (P2) amplitude. Thus, the observed age-related differences in the P22 (P2) amplitude are more likely associated with neurophysiological development rather than physical growth. Moreover, at the same C3′ electrode, not all SEP components show differences in amplitude among groups. It is possible that neurotransmitters involved in generating the potentials are related to these results, in addition to the generator sources of each component. Specifically, it is believed that gamma-aminobutyric acid (GABA) is associated with generation of the P22 (P2) component. GABA is a major inhibitory neurotransmitter in the brain and spinal cord, and is associated with ionic mechanisms of the inhibitory postsynaptic potential (IPSP) in cortical pyramidal neurons (Kandel et al., 2000). A previous study using the $GABA_A$ agonist lorazepam showed that the amplitude of P22 was significantly increased during paired-pulse paradigms (Stude et al., 2016). Therefore, the P22 (P2) component primarily reflects IPSP. On the other hand, the effect of lorazepam was not observed on the N18 (N1), suggesting that N18 (N1) is primarily driven by excitatory neurotransmitters generating excitatory postsynaptic potentials (EPSPs). Additionally, inhibitory mechanisms in cortices are considered to mature later than excitatory ones (Brooks-Kayal, 2005; Zanini et al., 2016), which is consistent with the results of this study. Based on these findings, although speculative, developmental neural mechanisms in GABA actions may be related to a decreasing the amplitude of P22 (P2) at C3′ with increasing age. Thus, the maturation of ionic mechanisms of IPSP in areas 1 and 4 was noted. However, further studies are needed to clarify the detailed neurochemical mechanisms, using paired-pulse paradigms in SEP recordings, which are often applied to investigate the automatic inhibitory function based on cortical GABA levels (Stude et al., 2016; Zanini et al., 2016;). Moreover, the amplitude of P22 (P2) among all participants weakly correlated with height (Table 3). This indicates that the amplitude of P22 (P2) decreases with both neural development in the brain and an increase in height as growth.

Takezawa et al. (2019) showed that elementary school children had P3 and N3 components between N27 (N2) and P45 (P4) at C3′. In the present study, although the occurrence rates of these two components were decreased in ADO, they still remained relatively high compared with CS (Table 2). Previous studies comparing the amplitudes of somatosensory high-frequency oscillations or SEPs between children and

**Table 3**
The r value of correlations between SEP components and height.

| Latency | | | Amplitude | | |
|---|---|---|---|---|---|
| Fz | P12 | 0.596*** | Fz | N15 | 0.030 |
| | N15 | 0.664*** | | P18 | −0.021 |
| | P18 | 0.636*** | | N30 | −0.024 |
| | N30 | 0.271** | | | |
| C3′ | P12 (P1) | 0.647*** | C3′ | N18 (N1) | −0.212* |
| | N18 (N1) | 0.690*** | | P22 (P2) | −0.215* |
| | P22 (P2) | 0.359*** | | N27 (N4) | 0.224* |
| | N27 (N4) | 0.215* | | P45 (P4) | 0.255* |
| | P45 (P4) | −0.126 | | N60 (N4) | 0.069 |
| | N60 (N4) | 0.110 | | | |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

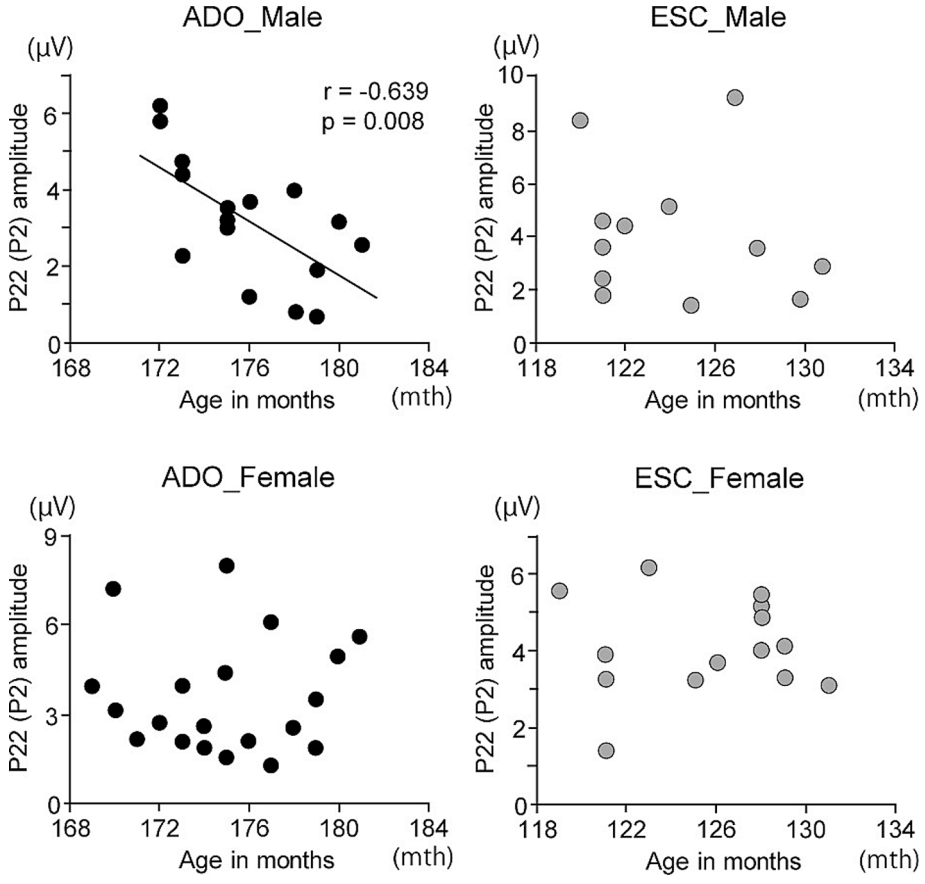


**Fig. 5.** Correlation between P22 (P2) amplitude at C3′ and age in months for ESC and ADO. ESC = elementary school children; ADO = adolescents.

adults reported that amplitudes in some components were larger in children than in adults (Nakano and Hashimoto, 2000; Takezawa et al., 2019; Zanini et al., 2016). These studies proposed the existence of immature inhibitory mechanisms in somatosensory processing in children. Furthermore, norepinephrine and serotonin are associated with the functioning of the sensory systems, including somatosensory, vision, and auditory (Hurley et al., 2004), and these neurotransmitters play important roles in regulating central nervous system development (Murrin et al., 2007). Additionally, previous studies using magnetic resonance imaging (MRI) have reported significant developmental changes in white matter from late childhood to adolescence (Lebel and Deoni, 2018). Taking these findings into consideration, differences in the characteristics of the somatosensory system by age in the present study suggest the involvement of age-dependent neurobiological changes associated with brain development. The present study could not clarify the generator mechanisms for P3 and N3 components at C3′, since we did not perform source analysis. As mentioned in Introduction, neural activity at C3′ is mainly generated from a posterior pathway in Brodmann's area 3b, areas 1 and 2 of SI (Cebolla et al., 2011; Inui et al., 2004). In addition, Barba and colleagues, utilizing depth electrodes in epilepsy patients, reported that the fronto-central N60 response originated from not only SI, but also SMA (Barba et al., 2008). Based on these findings, the maturation of neural activities including those at SI and SMA might be related to decreases in the occurrence of P3 and N3 components with increasing age.

The gray matter volume decreases throughout adolescence (Mills et al., 2016; Winkler et al., 2012). Additionally, Corrigan et al. (2021) reported that myelination in the parietal gray matter is significantly correlated with age. However, the white matter volume increases with age and this continues into adulthood (Herting et al., 2017; Mills et al., 2016). In the present study, the observed decrease in the P22 (P2) amplitude and the disappearance of P3 and N3 components with age may be influenced by the progression of myelin development, particularly in the parietal cortex, as well as by changes in the white matter volume that contribute to neural efficiency.

Females showed larger amplitudes of N15 at Fz than males in all groups (Fig. 3). Since no significant correlation was found between the amplitude of N15 and height, factors other than the height should be considered (Table 3). As noted above, N15 at Fz is generated from higher segments of the cervical cord, and at or near the foramen magnum (Cruccu et al., 2008; Restuccia et al., 1995). A previous study examining the brain structure in individuals aged 8 to 30 years showed that whole-brain and white matter volumes are larger in males than females (Mills et al., 2016), indicating that sex differences may be present not only in the cerebral cortex but also subcortical regions. Therefore, the smaller whole-brain and white matter volumes in females may have led to more efficient neural activity, resulting in a smaller amplitude. Since no previous studies examined sex differences in neural activity related to somatosensory processing (Boor et al., 1998; Takezawa et al., 2019; Taylor and Fagan, 1988; Zanini et al., 2016), further research is needed to clarify the detailed mechanisms underlying differences in somatosensory processing.

Correlation analyses between the amplitude of P22 (P2) at C3′ and age in months showed a significant negative correlation only in ADO boys, where the amplitude decreased with increasing age (Fig. 5). One of the indicators reflecting the peak of puberty is the age of peak height velocity (APHV). Yokoya and Higuchi. (2014) reported that APHV for Japanese children between 2006 and 2013 was 11.79 years for boys and 9.55 years for girls, with girls reaching the peak height velocity 2.04 years earlier than boys. Therefore, our data may reflect differences in development speed between boys and girls during puberty. Additionally, the lack of a significant correlation in both boys and girls in ESC suggests that they have not yet reached puberty at this stage, and thus, the neural basis involved in somatosensory processing is considered immature.

Research on neural activity related to somatosensory perception in children is expected to have various clinical applications in the future. Sensory-based therapies are being increasingly used by occupational therapists and sometimes by other types of therapists in the treatment of children with developmental and behavioral disorders, such as autism spectrum disorders, attention-deficit/hyperactivity disorder, and developmental coordination disorders (Zimmer and Desch, 2012). The present study mainly focused on somatosensory processing for healthy adolescents, but our findings might also help to understand the neural activity associated with somatosensory perception in children with these disorders.

The present study had several limitations. First, we could not directly check secondary physical sexual development or conduct hormonal examination in either male or female participants. Second, electrical stimulation applied only to the right median nerve in this study. To estimate interhemispheric differences in somatosensory processing, it would be better to stimulate both left and right median nerves and compare the resulting SEPs. Further investigation is necessary in the future.

In conclusion, we showed the characteristics of somatosensory processing in ESC, by comparing those among ADO and CS. Especially, the amplitude of P22 (P2) at C3′ decreased with increasing age, related to inhibitory neural activity. Furthermore, the occurrence of P3 and N3 components at C3′ decreases with age due to neurobiological changes associated with brain development. There was a significant correlation in ADO boys between the amplitude of P22 (P2) at C3′ and age in months, but not in ADO girls. These data suggest that the somatosensory processing in ADO is not as mature as in adults, and sex differences exist in somatosensory systems between ADO boys and girls.

## Author contributions

A.M., H.N., and M.S. conceived and designed research; A.M. and H. N. performed experiments; A.M. analyzed data; A.M., H.N., and M.S. interpreted results of experiments; A.M. and H.N. prepared figures; A. M., H.N., and M.S. drafted the manuscript; All authors approved the final version of the manuscript.

## Financial disclosure

This study was supported by the Sumitomo Electric Group CSR Foundation.

## CRediT authorship contribution statement

**Aoi Mase:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft. **Hiroki Nakata:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. **Manabu Shibasaki:** Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We would like to express our gratitude to the children and their families for participation in this study.

## Data availability

Data will be made available on request.

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