Effects of passive heat stress on human somatosensory processing

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Nakata H, Oshiro M, Namba, M, and Shibasaki M. Effects of passive heat stress on human somatosensory processing. Am J Physiol Regul Integr Comp Physiol 309: R1387–R1396, 2015. First published October 14, 2015; doi:10.1152/ajpregu.00280.2015.—Herein, we investigated the effects of passive heat stress on human somatosensory processing recorded by somatosensory-evoked potentials (SEPs). Fifteen healthy subjects received a median nerve stimulation at the left wrist under two thermal conditions: Heat Stress and normothermic Time Control. The latencies and amplitudes of P14, N20, P25, N35, P45, and N60 at C4’ and P14, N18, P22, and N30 at Fz were evaluated. Under the Heat Stress condition, SEPs were recorded at normothermic baseline (1st), early in heat stress (2nd), when esophageal temperature had increased by ~1.0°C (3rd) and ~2.0°C (4th), and after heat stress (5th). In the Time Control condition, SEPs were measured at the same time intervals as those in the Heat Stress condition. The peak latencies and amplitudes of SEPs did not change early in heat stress. However, the latencies of P14, N20, and N60 at C4’ and P14, N18, and P22 at Fz were significantly shorter in the 4th session than in the 1st session. Furthermore, the peak amplitudes of P25 and N60 at C4’, and P22 and N30 at Fz decreased with increases in body temperature. On the other hand, under the Time Control condition, no significant differences were observed in the amplitudes or latencies of any component of SEPs. These results suggested that the conduction velocity of the ascending somatosensory input was accelerated by increases in body temperature, and hyperthermia impaired the neural activity of cortical somatosensory processing.

AN EXCESSIVE INCREASE IN INTERNAL temperature (i.e., hyperthermia) has been suggested to impair exercise performance, such as maximal exercise endurance (4) and muscle contractions (33, 37), and these impairments have been attributed to hyperthermia-induced central fatigue. Recent studies using functional magnetic resonance imaging, event-related potentials, and evoked potentials have focused on brain functions during hyperthermia, and the findings showed that hyperthermia-induced central fatigue impaired cognitive function and led to a greater load in the frontal-parietal network to perform tasks (15, 20, 31, 51, 52).

In addition, several groups previously investigated the effects of hyperthermia on descending central processing, which is associated with motor commands through the corticospinal tract to target muscles (42, 43, 46, 48, 54). Transcranial magnetic stimulation (TMS) has been employed to assess the excitability of the corticospinal tract by exposing the scalp of human participants to a brief magnetic field over the primary motor cortex. Studies using TMS demonstrated that hyperthermia-induced central fatigue impaired descending central processing.

On the other hand, somatosensory-evoked potentials (SEPs), obtained by time-locked averaging EEG with high temporal resolution, have been used to evaluate ascending central processing (i.e., somatosensory processing). SEPs are elicited by stimulating peripheral nerves, such as the median nerve at the wrist. The latencies and amplitudes of the P14, N20, P25, N35, P45, and N60 components, which are recorded at centroparietal electrodes contralateral to the stimulated site, are then determined during the median nerve stimulation. N20 is the primary response from Brodmann’s area 3b of the primary somatosensory cortex, and the subsequent components recorded at around 20–60 ms are generated in areas 3b, 1, and 4 (1, 2, 19). The P14 component is recorded just before N20 and is generated from the subcortical region (8, 9, 27). The P22 and N30 components recorded at the frontal electrodes are generated from the primary motor cortex, premotor area, and prefrontal cortex (7, 35, 55). Some adventitious somatosensory inputs, such as voluntary or passive movements, interfering tactile stimuli, and water immersion in the perturbation, were found to attenuate the amplitudes of SEPs (8, 22, 24, 27, 28, 39, 49).

In animal studies, the latency of SEPs was shortened by body heating and then increased before the time of death due to excessive hyperthermia, whereas the amplitude did not change (32, 44, 45). Kazis et al. (25) demonstrated that hyperthermia had no effect on the latency and amplitude of N20 in humans. However, they examined subjects with fever (38.0–39.7°C) and compared their findings with a prognosis trial (i.e., when body temperature was returned to normal). The thermoregulatory mechanism underlying fever differs from that of passive heat exposure and/or exercise (38); therefore, the effects of hyperthermia on central neural processing may also differ between these conditions. These differences in species and thermogenesis, coupled with the inconsistent findings of other somatosensory stimulation studies, indicated that a mechanistic study is needed to determine whether exercise or heat stress-induced hyperthermia modulates ascending neural processing.

Therefore, the aim of the present study was to examine the effects of passive heat stress on human somatosensory processing by utilizing SEPs. We hypothesized that hyperthermia impaired the ascending central pathway/processing (i.e., somatosensory processing), as well as the neural descending pathway, as previously reported (42, 43, 46, 48, 54).

METHODS

Experiment 1 (Heat Stress)

Subjects. Fifteen male subjects (mean age 20.7 years, range 19–23) participated in this study. No subject had a history of a neurological or psychiatric disorder. The procedures used complied with the
Declarations of Helsinki regarding human experimentation, and the study was approved by the Ethics Committee of Nara Women’s University, Nara, Japan. All subjects gave their written informed consent to participate in the study.

Procedure. Experiments were performed in a temperature-controlled laboratory at 26°C. On arrival to the laboratory, the subjects weighed themselves nude on a scale and wore only underwear and short pants. Each subject inserted a copper-constantan thermocouple via the nasal passage to a distance equivalent to one-fourth of the subject’s height to measure esophageal temperature. Esophageal temperature was continuously measured and sampled at 20 Hz via an electrocardiogram (Biomulti 1000, NEC, Tokyo, Japan) and by auscultation of the brachial artery via electrosphygmomanometry (STBP-780, Colin, Tokyo, Japan). Mean skin temperatures were calculated from the weighted average of six points (53).

Body temperature was controlled by a tube-lined suit (Med-Eng, Ottawa, Ontario, Canada), which covered the entire body, except for the head, face, hands, and feet. Heart rate and intermittent arterial blood pressure were obtained from an electrocardiogram (Biometrics 30 min under normothermic conditions. Experiments were performed in a temperature-controlled laboratory at 26°C. On arrival to the laboratory, the subjects weighed themselves nude on a scale and wore only underwear and short pants. Each subject inserted a copper-constantan thermocouple via the nasal passage to a distance equivalent to one-fourth of the subject’s height to measure esophageal temperature. Esophageal temperature was continuously measured and sampled at 20 Hz via a data acquisition system (MP150, BIOPAC Systems, Santa Barbara, CA). Skin temperatures were measured at six sites (the chest, abdomen, upper and lower back, thigh, and calf). Skin temperatures were also continuously measured by thermocouples, but sampled at 1-s intervals via another data acquisition system (DA100, Yokogawa, Tokyo, Japan). Mean skin temperatures were calculated from the weighted average of six points (53).

Following instrumentation, subjects rested quietly in a semi-supine position on a hospital bed for ~30 min. Thermoneutral condition was maintained by perfusing 33°C water through the suit. During this equilibrium period, EEG electrodes were placed on the scalp and earlobes. Then, the baseline data of SEPs were recorded [i.e., 1st (pre) session]. Subjects were then exposed to heat stress by perfusing 50°C water through the suit, and SEPs were recorded after 10 min after the initiation of heat stress [2nd (early) session]. When esophageal temperature had increased by ~1.0°C, SEPs were recorded [3rd (middle) session]. Subjects were again exposed to heat stress until esophageal temperature had increased by 2.0°C, and SEPs were recorded after this temperature had been achieved [4th (severe) session]. After recording SEPs in the 4th session, cold water (25°C) was immediately perfused through the suit for recovery, and SEPs were again recorded after ~10 min [5th (post) session].

To record SEPs, the electric stimulus used was a constant current square-wave pulse delivered to the left median nerve at a rate of 3 Hz. The stimulus duration was 0.2 ms, and the stimulus intensity was sufficient to produce a slight, but definite, twitch of the thumb. Subjects were instructed to keep their eyes open and look at a small fixed point in front of them at a distance of ~1.5 m. Two hundred stimuli were applied in each session, and the length of the recording time was ~80 s in each session.

Experiment 2 (Time Control)

Long-term habituation and sleepiness have been suggested to decrease the amplitude of SEPs, especially middle-late latency SEPs (17, 41). Since passive heat stress trials generally take more than 2 h to complete, the present study also evaluated changes in SEPs for a prolonged trial. SEPs in the Time Control condition were recorded at the same time intervals as those in the Heat Stress condition.

Subjects. All fifteen subjects were the same as those in Experiment 1. There was at least a 3-day interval between Experiments 1 and 2, and the experiments were performed at the same time on a different day.

Procedure. To record SEPs under normothermic Time Control conditions, experiments were performed in the same laboratory as that for Experiment 1. The subject also dressed in the same water-perfused, tube-lined suit. After instrumentation, subjects laid supine on a hospital bed for ~30 min under normothermic conditions. Thermoneural conditions were maintained by perfusing 33°C water through the suit. After this equilibrium period, the baseline data of SEPs were recorded (i.e., 1st session). To record the SEPs of the 2nd, 3rd, 4th, and 5th sessions under Time Control conditions, the time intervals for each subject were set on the basis of the starting time of SEP recordings in Experiment 1, namely, the time interval between sessions in Experiment 2 was the same as that in Experiment 1. The starting time of the session was 12.1 ± 2.9 (SD) min in the 2nd session, 41.7 ± 7.0 min in the 3rd session, 75.7 ± 9.8 min in the 4th session, and 86.9 ± 9.5 min in the 5th session. The method used to record SEPs and statistical analyses were the same as those for Experiment 1.

EEG recordings. SEPs were recorded with Ag/AgCl disk electrodes placed on the scalp at Fz, Cz, Pz, and C4’ (C4’ was 2 cm posterior to C4), according to the International 10–20 System (Fig. 1). The C4’ electrode, which was located at the contralateral hemisphere to the left-hand stimulation, was used to record the neural activity of the primary somatosensory cortex. The Fz electrode was set to measure the neural activities generated by the primary motor cortex, premotor area, and prefrontal cortex. The Cz and Pz electrodes were supplementarily used to determine the peak amplitudes and latencies of each component at C4’ and Fz. Each electrode was referenced to linked earlobes. To eliminate eye movements or blinks exceeding 100 μV, an electrooculogram was recorded bilaterally 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. Impedance was maintained at less than 5,000 Ohm. All EEG signals were collected on a signal processor (Neuropack MEB-2200 system, Nihon-Kohden, Tokyo, Japan). The band-pass filter of the amplifier was 1-1,500 Hz. The analysis time was 100 ms, and sampling rate was 5,000 Hz.

Data and statistical analyses. A 60-s average was calculated for thermoregulatory variables and heart rate before and after each SEP recording. These values and mean blood pressure were averaged between, before, and after recordings. Thermoregulatory variables (i.e., esophageal and mean skin temperatures) and hemodynamic variables (i.e., heart rate and mean arterial pressure) were analyzed by a two-way ANOVA with repeated measures using the within-subject factors of condition (Heat Stress vs. Time Control) and session (1st, 2nd, 3rd, 4th, and 5th). The peaks of all recognizable components in SEPs were measured, and the peak amplitude of each component was identified immediately prior (i.e., peak-to-peak). On the basis of previous studies, we focused on the C4’ and Fz electrodes (39, 40). The peak latencies at C4’ were identified in P14, N20, P25, N35, P45, and N60 components, and peak amplitudes were measured for N20.
ASCENDING CENTRAL PROCESSING IN HYPERTHERMIA

Table 1. Thermal variables in Experiments 1 (Heat Stress) and 2 (Time Control)

<table>
<thead>
<tr>
<th>Condition</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>ANOVA for C-S interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal temp. °C</td>
<td>Heat 37.0 (0.2)</td>
<td>37.0 (0.2)</td>
<td>37.9 (0.3)***</td>
<td>38.9 (0.1)***</td>
<td>37.6 (0.3)***</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Control 36.7 (0.5)</td>
<td>36.6 (0.5)#</td>
<td>36.6 (0.3)###</td>
<td>36.7 (0.2)###</td>
<td>36.7 (0.2)###</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Mean skin temp. °C</td>
<td>Heat 33.8 (0.6)</td>
<td>37.9 (0.5)***</td>
<td>38.6 (0.5)***</td>
<td>39.4 (0.2)***</td>
<td>35.1 (0.5)***</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Control 34.3 (0.3)#</td>
<td>34.3 (0.5)###</td>
<td>34.4 (0.3)###</td>
<td>34.3 (0.3)###</td>
<td>34.3 (0.3)##</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>Heat 61.7 (11.9)</td>
<td>67.8 (10.5)**</td>
<td>92.8 (10.2)***</td>
<td>117.6 (11.1)***</td>
<td>83.8 (10.6)***</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Control 60.1 (10.8)</td>
<td>60.0 (9.8)###</td>
<td>59.0 (9.5)###</td>
<td>57.0 (9.9)###</td>
<td>59.5 (9.1)###</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>Heat 99.0 (9.4)</td>
<td>97.2 (8.7)</td>
<td>98.9 (11.4)</td>
<td>97.8 (10.4)</td>
<td>100.6 (13.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Control 95.0 (5.9)</td>
<td>94.1 (9.1)</td>
<td>97.4 (6.4)</td>
<td>95.2 (5.9)</td>
<td>94.0 (6.8)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data were expressed as the mean (SD). Post hoc results versus the 1st session ***P < 0.001; Significant differences (Heat versus Control) #P < 0.05, ##P < 0.01, and ###P < 0.001. C-S: Condition-Session.

(P14-N20), P25 (N20-P25), N35 (P25-N35), P45 (N35-P45), and N60 (P45-N60). The peak latencies at Fz were identified in P14, N18, P22, and N30 components, and peak amplitudes were measured for N18 (P14-N18), P22 (N18-P22), and N30 (P22-N30). Data were separately submitted to a two-way ANOVA with condition and session as factors. In all repeated-measures factors, we tested whether Mauchly’s sphericity assumption was violated. If the result of Mauchly’s test was significant and the assumption of sphericity was violated, the Greenhouse-Geisser adjustment was used to correct sphericity by altering the degrees of freedom using a correction coefficient epsilon. Significant and the assumption of sphericity was violated, the Greenhouse-Geisser correction; \( F(2.455, 34.373) = 3.976, P < 0.05, \varepsilon = 0.614 \).

Further analyses for session showed a significant main effect during the Heat Stress condition [Greenhouse-Geisser correction; \( F(2.275, 31.844) = 5.172, P < 0.01, \varepsilon = 0.569 \)], but not

RESULTS

Table 1 shows esophageal and mean skin temperatures, heart rate, and mean arterial pressure under the Heat Stress and Time Control conditions. In the Heat Stress condition, whole body heating increased thermoregulatory variables and heart rate while maintaining mean arterial pressure, and subsequent whole body cooling decreased thermoregulatory variables and heart rate. In the Time Control condition, no significant changes were observed in esophageal temperature, mean skin temperature, heart rate, or mean arterial pressure.

Figures 2 and 3 show grand-averaged SEP waveforms at C4′ in Experiments 1 (Heat Stress) and 2 (Time Control), respectively, and the P14, N20, P25, N35, P45, and N60 components were determined. Figures 4 and 5 show the grand-averaged SEP waveforms at Fz in Experiments 1 and 2, respectively, and the P14, N18, P22, and N30 components were detected.

**Peak latency of SEPs.** ANOVAs for the peak latency of P14 at C4′ showed the significant main effects of condition [\( F(1, 14) = 16.183, P < 0.01 \)] and session [\( F(4, 56) = 4.325, P < 0.05 \)]. Further analyses for session revealed a significant main effect during the Heat Stress condition [\( F(4, 56) = 7.040, P < 0.001 \)], but not during the Time Control condition. The post hoc test showed that the peak latency of P14 was significantly shorter in the 4th and 5th sessions than in the 1st session during the Heat Stress condition [\( t(14) = 3.761, P < 0.01; t(14) = 2.873, P < 0.05 \)]. Further analyses for condition demonstrated that the peak latency of P14 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 4th session [\( F(1, 14) = 11.502, P < 0.01 \)].

ANOVA for the peak latency of N20 at C4′ revealed the significant main effect of condition [\( F(1, 14) = 15.461, P < 0.01 \)] and a condition-session interaction [Greenhouse-Geisser correction; \( F(2.455, 34.373) = 3.976, P < 0.05, \varepsilon = 0.614 \)]. Further analyses for session showed a significant main effect during the Heat Stress condition [Greenhouse-Geisser correction; \( F(2.275, 31.844) = 5.172, P < 0.01, \varepsilon = 0.569 \)], but not

Fig. 2. Grand-averaged somatosensory-evoked potentials (SEP) waveforms in each session at C4′ under the Heat Stress condition. Black lines indicate waveforms in the 1st session, and gray lines show waveforms in the 2nd, 3rd, 4th, and 5th sessions. Asterisks (*) show components with peak latencies that were significantly shorter than those in the 1st session. Sharps (#) show components with peak amplitudes that were significantly smaller than those in the 1st session.
during the Time Control condition. The post hoc test showed that the peak latency of N20 was significantly shorter in the 4th and 5th sessions than in the 1st session during the Heat Stress condition ($t(14) = 3.070, P < 0.01$; $t(14) = 4.593, P < 0.001$). Further analyses for condition demonstrated that the peak latency of N20 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 3rd ($F(1, 14) = 14.558, P < 0.01$), 4th ($F(1, 14) = 12.817, P < 0.01$), and 5th sessions ($F(1, 14) = 12.495, P < 0.01$).

ANOVA for the peak latency of N35 at C4 revealed a significant condition-session interaction [$F(4, 56) = 3.123, P = 0.07$, $\varepsilon = 0.413$]. Further analyses for condition demonstrated that the peak latency of N35 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 3rd ($F(1, 14) = 5.633, P < 0.05$), 4th ($F(1, 14) = 9.728, P < 0.01$), and 5th sessions ($F(1, 14) = 27.555, P < 0.001$).

ANOVA for the peak latency of N60 at Fz showed the significant main effect of session [$F(4, 56) = 15.276, P < 0.01$] and a condition-session interaction [$F(4, 56) = 2.988, P < 0.05$]. Further analyses for condition showed a significant main effect during the Heat Stress condition [$F(4, 56) = 7.384, P < 0.001$], but not during the Time Control condition. The post hoc test indicated that the peak latency of N60 was significantly shorter in the 4th and 5th sessions than in the 1st session [$t(14) = 3.070, P < 0.01$; $t(14) = 4.593, P < 0.001$]. Further analyses for condition demonstrated that the peak latency of N60 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 3rd [$F(1, 14) = 14.558, P < 0.01$], 4th [$F(1, 14) = 12.817, P < 0.01$], and 5th sessions [$F(1, 14) = 12.495, P < 0.01$].

ANOVA for the peak latency of P14 at Fz showed the significant main effect of session [$F(4, 56) = 3.810, P <
Further analyses for session showed a significant main effect during the Heat Stress condition [Greenhouse-Geisser correction; \( F(1, 14) = 2.428, P < 0.05; t(14) = 6.049, P < 0.001 \)]. Further analyses for condition demonstrated that the peak latency of N18 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 3rd \( [F(1, 14) = 9.893, P < 0.01] \) and 4th sessions \( [F(1, 14) = 51.048, P < 0.001] \).

ANOVA for the peak latency of P22 at Fz revealed the significant main effects of condition \( [F(1, 14) = 21.668, P < 0.001] \) and session [Greenhouse-Geisser correction; \( F(2.170, 30.386) = 6.023, P < 0.01, \text{\( \varepsilon = 0.543 \)} \), and a condition-session interaction [Greenhouse-Geisser correction; \( F(1.743, 24.396) = 3.731, P < 0.05, \text{\( \varepsilon = 0.436 \)} \). Further analyses for session showed a significant main effect during the Heat Stress condition [Greenhouse-Geisser correction; \( F(1.766, 24.724) = 5.640, P < 0.05, \text{\( \varepsilon = 0.442 \)} \), but not during the Time Control condition. The post hoc test showed that the peak latency of P22 was significantly shorter in the 3rd and 4th sessions than in the 1st session during the Heat Stress condition \( [t(14) = 3.226, P < 0.01; t(14) = 5.808, P < 0.001] \). Further analyses for condition showed that the peak latency of P22 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 3rd \( [F(1, 14) = 10.832, P < 0.01] \) and 4th sessions \( [F(1, 14) = 92.876, P < 0.001] \).

ANOVA for the peak latency of N30 at Fz revealed the significant main effect of condition \( [F(1, 14) = 6.575, P < 0.05] \). Further analyses for condition demonstrated that the peak latency of N30 was significantly shorter during the Heat Stress condition than during the Time Control condition in the 3rd \( [F(1, 14) = 7.195, P < 0.05] \) and 5th sessions \( [F(1, 14) = 9.460, P < 0.05] \). There were no significant main effects or interaction in the peak latencies of P25 at C4’ (Table 2).

**Peak amplitude of SEPs.** ANOVAs for the peak amplitude of P25 at C4’ revealed the significant main effect of condition \( [F(1, 14) = 5.950, P < 0.05] \) and a condition-session interaction \( [F(4, 56) = 5.097, P < 0.01] \). Further analyses for session showed a significant main effect during the Heat Stress condition [Greenhouse-Geisser correction; \( F(2.581, 36.129) = 3.833, P < 0.05, \text{\( \varepsilon = 0.645 \)} \), but not during the Time Control. The post hoc test showed that the amplitude of P25 was significantly smaller in the 4th and 5th sessions than in the 1st session \( [t(14) = 3.058, P < 0.01; t(14) = 2.169, P < 0.05, \text{respectively}] \). Further analyses for condition demonstrated that the peak amplitude of P25 was significantly smaller during the Heat Stress condition than during the Time Control condition in the 3rd \( [F(1, 14) = 5.168, P < 0.05] \), 4th \( [F(1, 14) = 11.370, P < 0.01] \), and 5th sessions \( [F(1, 14) = 7.202, P < 0.05] \).

ANOVA for the peak amplitude of P45 at C4’ showed a strong tendency of the significant main effect of session \( [F(4, 56) = 2.466, P = 0.055] \). ANOVAs for the peak amplitude of N60 at C4’ showed the significant main effects of condition \( [F(1, 14) = 9.621, P < 0.01] \) and session [Greenhouse-Geisser correction; \( F(2.393, 33.498) = 3.480, P < 0.05, \text{\( \varepsilon = 0.598 \)} \), and a condition-session interaction [Greenhouse-Geisser correction; \( F(1.820, 25.474) = 4.290, P < 0.05, \text{\( \varepsilon = 0.455 \)} \).

Further analyses for session showed a significant main effect during the Heat Stress condition [Greenhouse-Geisser correction; \( F(2.015, 28.214) = 6.257, P < 0.01, \text{\( \varepsilon = 0.504 \)} \), but not during the Time Control condition. The post hoc test indicated that the peak amplitude of N60 was significantly smaller in the

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**Fig. 5.** Grand-averaged ERP waveforms in each session at Fz under the time control condition. Black lines indicate waveforms in the 1st session, and gray lines show waveforms in the 2nd, 3rd, 4th, and 5th sessions. No significant differences were observed in the amplitude or latency of any component between any sessions.
Table 2. Peak latencies of somatosensory evoked potentials and statistical results at C4' and Fz

<table>
<thead>
<tr>
<th>Condition</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4'</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P14</td>
<td>Heat</td>
<td>14.6 (0.3)</td>
<td>14.4 (0.2)</td>
<td>14.0 (0.2)</td>
<td>13.3 (0.3)**</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>14.6 (0.2)</td>
<td>14.6 (0.2)</td>
<td>14.3 (0.2)</td>
<td>14.3 (0.3)##</td>
</tr>
<tr>
<td>N20</td>
<td>Heat</td>
<td>19.1 (0.2)</td>
<td>19.4 (0.5)</td>
<td>18.6 (0.3)</td>
<td>18.2 (0.3)**</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>19.2 (0.3)</td>
<td>18.9 (0.3)</td>
<td>19.1 (0.3)#</td>
<td>19.3 (0.3)##</td>
</tr>
<tr>
<td>P25</td>
<td>Heat</td>
<td>23.5 (0.5)</td>
<td>24.2 (0.8)</td>
<td>23.5 (0.6)</td>
<td>23.4 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>23.5 (0.5)</td>
<td>23.7 (0.5)</td>
<td>24.1 (0.7)</td>
<td>23.8 (0.8)</td>
</tr>
<tr>
<td>N35</td>
<td>Heat</td>
<td>33.5 (1.1)</td>
<td>33.9 (1.2)</td>
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<td>31.6 (1.0)</td>
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<tr>
<td></td>
<td>Control</td>
<td>31.8 (1.1)</td>
<td>31.5 (1.0)</td>
<td>32.8 (0.7)</td>
<td>33.4 (1.3)</td>
</tr>
<tr>
<td>P45</td>
<td>Heat</td>
<td>45.8 (0.9)</td>
<td>46.2 (0.9)</td>
<td>45.0 (1.1)</td>
<td>42.9 (1.0)</td>
</tr>
<tr>
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<td>Control</td>
<td>43.8 (1.3)</td>
<td>44.2 (1.5)</td>
<td>44.6 (1.5)</td>
<td>45.4 (1.3)</td>
</tr>
<tr>
<td>Fz</td>
<td></td>
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<tr>
<td>P14</td>
<td>Heat</td>
<td>14.6 (0.3)</td>
<td>14.2 (0.2)</td>
<td>13.9 (0.2)</td>
<td>13.3 (0.2)**</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>14.3 (0.2)</td>
<td>14.5 (0.2)</td>
<td>14.0 (0.1)</td>
<td>14.2 (0.2)</td>
</tr>
<tr>
<td>N18</td>
<td>Heat</td>
<td>17.6 (0.4)</td>
<td>17.2 (0.2)</td>
<td>16.6 (0.2)*</td>
<td>15.9 (0.2)##</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>17.3 (0.2)</td>
<td>17.0 (0.1)</td>
<td>17.4 (0.2)##</td>
<td>17.2 (0.3)##</td>
</tr>
<tr>
<td>P22</td>
<td>Heat</td>
<td>20.1 (0.4)</td>
<td>20.0 (0.3)</td>
<td>19.3 (0.4)**</td>
<td>18.1 (0.2)**#</td>
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<tr>
<td></td>
<td>Control</td>
<td>20.2 (0.4)</td>
<td>19.8 (0.2)</td>
<td>20.0 (0.3)##</td>
<td>19.9 (0.3)###</td>
</tr>
<tr>
<td>N30</td>
<td>Heat</td>
<td>31.1 (0.9)</td>
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<td>28.3 (1.0)</td>
<td>29.2 (1.0)</td>
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<td>Control</td>
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<td>31.0 (1.1)</td>
<td>31.9 (1.2)#</td>
<td>31.2 (1.0)</td>
</tr>
</tbody>
</table>

Data were expressed as the mean (SE). Post hoc results versus the 1st session *P < 0.05, **P < 0.01, and ***P < 0.001; Significant differences (Heat versus Control) #P < 0.05, ##P < 0.01, and ###P < 0.001.

3rd and 4th sessions than in the 1st session [t (14) = 3.485, P < 0.01; t (14) = 3.153, P < 0.01, respectively]. Further analyses for condition demonstrated that the peak amplitude of N60 was significantly smaller during the Heat Stress condition than during the Time Control condition in the 3rd [F (1, 14) = 6.329, P < 0.05], 4th [F (1, 14) = 10.771, P < 0.01], and 5th sessions [F (1, 14) = 8.709, P < 0.05].

ANOVA for the peak amplitude of P22 at Fz showed the significant main effects of condition [F (1, 14) = 11.004, P < 0.01] and session [F (4, 56) = 4.739, P < 0.01]. Further analyses for session showed a significant main effect during the Heat Stress condition [F (4, 56) = 5.501, P < 0.01], but not during the Time Control. The post hoc test indicated that the peak amplitude of P22 at Fz was significantly smaller in the 3rd session than in the 1st session during the Heat Stress condition [t (14) = 2.564, P < 0.05]. Further analyses for condition demonstrated that the peak amplitude of P22 was significantly smaller during the Heat Stress condition than during the Time Control condition in the 3rd session [F (1, 14) = 7.901, P < 0.05].

ANOVA for the peak amplitude of N30 at Fz showed the significant main effects of condition [F (1, 13) = 10.510, P < 0.01] and session [F (4, 52) = 10.054, P < 0.001]. Further analyses for session showed a significant main effect during the Heat Stress condition [F (4, 52) = 7.996, P < 0.001], but not during the Time Control. The post hoc test indicated that the peak amplitude of N30 at Fz was significantly smaller in the 3rd, 4th, and 5th sessions than in the 1st session during the Heat Stress condition [t (14) = 2.683, P < 0.05; t (13) = 4.046, P < 0.01; t (14) = 3.514, P < 0.01, respectively]. Further analyses for condition demonstrated that the peak amplitude of N30 was significantly smaller during the Heat Stress condition than during the Time Control condition in the 3rd [F (1, 14) = 14.231, P < 0.01], 4th [F (1, 13) = 6.707, P < 0.05], and 5th sessions [F (1, 14) = 5.384, P < 0.05]. There were no significant main effects or interactions in the peak amplitudes of N20 or N35 at C4' or N18 at Fz (Table 3). No significant correlational relationships were observed between changes in the amplitudes and latencies at P25, N35, P45, and N60 at C4' and P22 and N30 at Fz.

DISCUSSION

Herein, we showed the effects of hyperthermia on human somatosensory processing using SEPs. The peak latencies of P14, N20, and N60 at C4' and P14, N18, and P22 at Fz were significantly shortened by increases in body temperature, suggesting that ascending signals from the periphery to the primary somatosensory cortex were accelerated. On the other hand, the peak amplitudes of P25 and N60 at C4' and P22 and N30 at Fz decreased with increases in body temperature, indicating a reduction in neural activities in human somatosensory processing during hyperthermia.

Effects of hyperthermia on amplitudes of SEPs. The primary response of SEPs was recorded ~20 ms after stimulating the median nerve and was referred to as the N20 component. This component is generated from Brodmann’s area 3b of the primary somatosensory cortex, and its latency has been used as an index of the conduction velocity of the peripheral somatosensory pathway from the median nerve to the primary somatosensory cortex. The amplitude of N20 did not change throughout heat stress, suggesting that the primary response to the stimulation of the median nerve was similar throughout experiments and also that electrical noise due to sweating during this perturbation did not affect EEG electrodes.

Somatosensory input from the primary somatosensory cortex is known to be serially processed through two pathways: to the posterior parietal cortex (i.e., to areas 3b, 1, 2, 5, and 7) and to the secondary somatosensory cortex (i.e., to areas 3b, 1, 2, and the secondary somatosensory cortex) (1, 2, 19). A previous study using dipole modeling with magnetoencephalography also identified multiple cortical areas as generators at ~20–60
ms, involving areas 3b, 1, 4, and the posterior parietal cortex (19). It is considered important to determine why the amplitudes of P25 and N60 were decreased during hyperthermia. SEP components after ~30–40 ms have been related to endo- genetic and attentional electrogenesis because they are influenced by target and nontarget effects, as well as distraction (11). Decreases in the amplitudes of P25 and N60 may not be associated with reductions in arousal and habituation because these components were not changed under the Time Control condition (Experiment 2) (Figs. 3 and 5, Table 3). Although the generator mechanisms of all SEPs components remain unknown, we assumed that the generator mechanisms of P25 and N60 were easily affected by various somatosensory inputs, including heat sensation and motor commands within the cortex, and that not all components of SEPs generated from areas 3b, 1, 2, and 4 and the posterior parietal cortex (i.e., areas 5 and 7) were modulated by ascending and descending neural processes. Previous studies reported a decrease in the amplitude of P25 and no change in the amplitude of N20 during voluntary movement (8, 27, 28, 39), passive movement (39), movement preparation (26), muscle relaxation (56), movement contralateral to the stimulated hand (30), and interfering tactile stimuli (22, 24). Furthermore, a decrease in the amplitude of N60 and no change in the amplitude of N35 were observed during movement preparation (26). Sato et al. (49) also reported that the amplitudes of only the P25 and P45 components were reduced during water immersion and suggested that a multimodal somatosensory stimulation, such as water pressure and thermal sensation, affected the neural activity of somatosensory processing. In the present study, in the early stage of passive heat stress (i.e., 2nd session), mean skin temperature increased without a change in esophageal temperature, whereas the amplitudes of P25 and P45 did not change (Table 3), suggesting that thermal inputs from skin thermoreceptors did not modulate ascending central processing. However, a significant reduction was observed in the amplitudes of P25 and N60 at C4' when esophageal temperature was elevated further. Taken together, these results indicated that heat stress-induced hyperthermia impaired ascending central processing.

Regarding neural activities at the frontal electrode, the peak amplitudes of P22 and N30 at Fz were significantly decreased by increases in body temperature, whereas N18 remain unchanged (Table 3). These results indicated that an impairment occurred at the cortical, but not the subcortical, level. The generator sources of P22 and N30 at Fz have been identified as independent generators from parietal SEP components (i.e., N20, P25, N35, P45, and N60 at C4'). Early frontal components have been detected in the primary motor cortex, premotor area, and prefrontal cortex based on source estimation (7), clinical data (35), and TMS (55). N18 has been recorded as a far-field component that is generated from the subcortical level (27). In addition to SEP components at centro-parietal electrodes contralateral to the stimulated site, the frontal SEP components at Fz were shown to be decreased during voluntary and passive movements (39), movement preparation (26), motor imagery (10), intention not to move (16), and light superficial and deep muscular massage (9). These findings together with our results suggest that hyperthermia affects neural activities related to somatosensory processing in some regions, such as the primary somatosensory cortex, primary motor cortex, premotor area, and prefrontal cortex.

Previous studies focused on the effects of hyperthermia on the descending pathway from the central nervous system to target muscles (42, 43, 46, 48, 54). Nybo and Nielsen (42) demonstrated that the ability to sustain force production during prolonged voluntary contractions was markedly impaired by hyperthermia. These findings and the results of the present study showed that hyperthermia impaired neural activities for motor execution (i.e., descending) and somatosensory processing (i.e., ascending). Hyperthermia has been shown to be associated with a decrease in cerebral blood flow using transcranial Doppler and is mainly caused by hypocapnia followed by hyperthermia-induced hyperventilation (6, 58). Since brain functions require an adequate supply of oxygen and glucose, hypocapnia-induced vasoconstriction during hyperventilation under normothermic conditions was previously reported to inhibit neural activity-evoked flow responses (50). Therefore, hyperthermia-induced reductions in cerebral perfusion may

### Table 3. Peak amplitudes of somatosensory evoked potentials and statistical results at C4' and Fz

<table>
<thead>
<tr>
<th>Condition</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C4’</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N20 Heat</td>
<td>2.3 (0.2)</td>
<td>2.4 (0.2)</td>
<td>2.3 (0.2)</td>
<td>2.3 (0.2)</td>
<td>2.5 (0.3)</td>
</tr>
<tr>
<td>Control</td>
<td>2.3 (0.3)</td>
<td>2.4 (0.3)</td>
<td>2.6 (0.3)</td>
<td>2.7 (0.3)</td>
<td>2.4 (0.3)</td>
</tr>
<tr>
<td>P25 Heat</td>
<td>3.6 (0.5)</td>
<td>3.3 (0.4)</td>
<td>2.9 (0.4)</td>
<td>2.7 (0.3)**</td>
<td>3.0 (0.4)*</td>
</tr>
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<td>3.4 (0.4)</td>
<td>3.3 (0.4)#</td>
<td>3.8 (0.5)**</td>
<td>3.7 (0.4)#</td>
</tr>
<tr>
<td>N35 Heat</td>
<td>2.7 (0.4)</td>
<td>2.6 (0.4)</td>
<td>2.4 (0.4)</td>
<td>2.4 (0.3)</td>
<td>2.3 (0.3)</td>
</tr>
<tr>
<td>Control</td>
<td>2.5 (0.4)</td>
<td>2.7 (0.4)</td>
<td>2.6 (0.4)</td>
<td>2.4 (0.4)</td>
<td>2.4 (0.5)</td>
</tr>
<tr>
<td>P45 Heat</td>
<td>3.4 (0.5)</td>
<td>3.5 (0.3)</td>
<td>3.1 (0.3)</td>
<td>2.6 (0.3)</td>
<td>3.0 (0.3)</td>
</tr>
<tr>
<td>Control</td>
<td>3.4 (0.4)</td>
<td>3.4 (0.4)</td>
<td>3.6 (0.4)</td>
<td>3.2 (0.3)</td>
<td>3.3 (0.3)</td>
</tr>
<tr>
<td>N60 Heat</td>
<td>4.7 (0.6)</td>
<td>4.8 (0.6)</td>
<td>4.0 (0.5)**</td>
<td>3.2 (0.3)**</td>
<td>3.9 (0.4)</td>
</tr>
<tr>
<td>Control</td>
<td>4.8 (0.5)</td>
<td>4.7 (0.4)</td>
<td>4.8 (0.4)#</td>
<td>4.8 (0.5)**</td>
<td>4.9 (0.5)#</td>
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<tr>
<td><strong>Fz</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N18 Heat</td>
<td>1.6 (0.2)</td>
<td>1.8 (0.1)</td>
<td>1.4 (0.1)</td>
<td>1.5 (0.1)</td>
<td>1.6 (0.2)</td>
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<tr>
<td>Control</td>
<td>1.5 (0.2)</td>
<td>1.6 (0.1)</td>
<td>1.6 (0.2)</td>
<td>1.5 (0.1)</td>
<td>1.6 (0.2)</td>
</tr>
<tr>
<td>P22 Heat</td>
<td>1.4 (0.1)</td>
<td>1.6 (0.2)</td>
<td>1.1 (0.1)#*</td>
<td>1.2 (0.1)</td>
<td>1.4 (0.1)</td>
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<tr>
<td>Control</td>
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<td>1.6 (0.2)</td>
<td>1.4 (0.2)#</td>
<td>1.4 (0.2)</td>
<td>1.5 (0.2)</td>
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<td>N30 Heat</td>
<td>4.3 (0.4)</td>
<td>4.4 (0.4)</td>
<td>3.5 (0.4)*</td>
<td>3.1 (0.2)**</td>
<td>3.4 (0.3)**</td>
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<tr>
<td>Control</td>
<td>4.5 (0.4)</td>
<td>4.7 (0.4)</td>
<td>4.5 (0.4)#</td>
<td>4.0 (0.4)#</td>
<td>4.1 (0.3)#</td>
</tr>
</tbody>
</table>

Data were expressed as the mean (SE). Post hoc results versus the 1st session *P < 0.05, and **P < 0.01; Significant differences (Heat versus Control) #P < 0.05, and ##P < 0.01.
reduce neural activity in processing after a neural input into the primary somatosensory cortex. Blood oxygen level-dependent MRI revealed that most of the cerebral vasculature is sensitive to carbon dioxide, whereas negative cerebrovascular responses to carbon dioxide have been observed in some regions (12). These regional differences in brain blood flow distribution may have contributed to variations in the changes observed in the amplitude of SEPs. Further studies are needed to clarify this issue.

Effects of hyperthermia on latencies of SEPs. The peak latencies of P14, N20, and N60 at C4’ and P14, N18, and P22 at Fz were shortened by increases in body temperature in Experiment 1 (Figs. 2 and 4, and Table 2), whereas this phenomenon was not observed in Experiment 2 (Time Control) (Figs. 3 and 5, and Table 2). As described above, because not only N20 at C4’, but also the far-field potentials of P14 at C4’ and P14 and N18 at Fz were shortened, the effects of passive heat stress were observed at the cortical and subcortical levels.

That is, ascending signals from the periphery to the primary somatosensory cortex may have been accelerated, which is consistent with previous findings obtained using rats (32, 44, 45). Therefore, to the best of our knowledge, this is the first study to demonstrate that ascending signals in human somatosensory processing were accelerated by increases in body temperature. The conduction time of SEPs is the sum of the axonal conduction and synaptic transmission times and has been suggested to be influenced by temperature (34). Therefore, the conduction velocity of the ascending somatosensory input may have been accelerated by increases in body temperature, and the effects of passive heat stress on the peak latency of SEPs continued even when skin temperature was sufficiently decreased after cooling.

In addition, it is important to consider why the peak latency of N60 at C4’ was significantly shorter in the 4th and 5th sessions than in the 1st session and also why no significant differences were observed in the peak latencies of P25, N35, and P45 at C4’ and N30 at Fz between sessions. We proposed the following explanation. The average data for the peak latencies of N35 and P45 at C4’ and N30 at Fz were clearly shorter in the 4th session than in the 1st session (Table 2). Therefore, the statistical power may have been weak in these components. A one-way ANOVA using the factor of session for the Heat Stress condition showed strong tendency of session in N35 at C4’, and the significant main effect of session in P45 at C4’ \( [F (4, 56) = 6.971, P < 0.001] \) and in N30 at Fz [Greenhouse-Geisser correction; \( F (2.278, 29.609) = 3.862, P = 0.028, \epsilon = 0.569 \)]. However, this explanation cannot be applied to the peak latency of P25 at C4’. We assumed that the P25 component reflected different neural processing from the N20 component. While N20 is generated from area 3b of the primary somatosensory cortex, P25 is generated from area 1 (3, 19). Anatomical studies demonstrated that area 1 received direct thalamocortical connections from the ventral lateral nucleus, and was also connected to area 3b (21, 23). On the other hand, area 3b mainly received connections from the ventral lateral nucleus. Therefore, differences in generating mechanisms may be related to the varying effects of passive heat stress on the peak amplitudes and latencies of N20 and P25 components.

Limitations of the present study. Although we showed reductions in some SEP components during passive heat stress in the present study, we did not evaluate actual perception and cognition of the somatosensory stimulus using psychophysical methods. The decrease observed in peak amplitudes in P25 and N60 at C4’ and P22 and N30 at Fz may affect cognitive function. The relationship between reductions in SEPs and actual cognitive performance needs to be examined in future studies. Moreover, in the present study, the same intensity of the median nerve stimulation was used throughout the experiment. However, if a different intensity of somatosensory stimuli had been performed in each session depending on sensory threshold, the changes of amplitudes of SEPs may have been observed.

Perspectives and Significance

Heat-related illness is a serious issue for the health of populations worldwide. This study demonstrated a new approach utilizing SEPs that contributes to a deeper understanding of the neural mechanisms underlying heat-related illness. The present study showed that hyperthermia impaired the neural activity of human cortical somatosensory processing. In addition, ascending signals from the periphery to the cortex were accelerated by increases in body temperature.

Since we used an electrical stimulation at 3 Hz delivered to the left median nerve, we were unable to record long-latency SEP components, such as P100 and N140. Previous studies using SEPs and somatosensory-evoked magnetic fields by time-locked averaging magnetoencephalography reported that long-latency components were generated from several regions, including the secondary somatosensory cortex, insula, cingulate cortex, and medial temporal area (18, 29), and the amplitudes of the secondary somatosensory cortex responses depended on the stimulus repetition rate, with a longer interstimulus interval eliciting a larger amplitude (13, 14, 57). Therefore, it was not possible to record long-latency SEP components in the experimental setting used in the present study. The secondary somatosensory cortex is related to a higher level of cognitive function in somatosensory processing, such as attention, decision-making, objective recognition, and the integration of nociceptive and nonnociceptive inputs (36, 47). Further studies are needed to clarify the effects of passive heat stress on long-latency SEP components.

A preventable methodology for impairment of human cognitive function, such as effective cooling and drinking, should be established in future studies.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: H.N., M.N., and M.S. conception and design of research; H.N., M.O., M.N., and M.S. performed experiments; H.N. and M.O. analyzed data; H.N. and M.S. interpreted results of experiments; H.N. prepared figures; H.N. and M.S. drafted manuscript; H.N. and M.S. edited and revised manuscript; H.N., M.O., M.N., and M.S. approved final version of manuscript.

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