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Effects of face/head and whole body cooling during passive heat stress on human somatosensory processing

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Running title: Effects of cooling on human somatosensory processing

Abstract

We herein investigated the effects of face/head and whole body cooling during passive heat stress on human somatosensory processing recorded by somatosensory-evoked potentials (SEPs) at C4' and Fz electrodes. Fourteen healthy subjects received a median nerve stimulation at the left wrist. SEPs were recorded at normothermic baseline (Rest), when esophageal temperature had increased by ~1.2 °C (Heat stress: HS) during passive heating, face/head cooling during passive heating (face/head cooling: FHC), and after HS (whole body cooling: WBC). The latencies and amplitudes of P14, N20, P25, N35, P45, and N60 at C4' and P14, N18, P22, and N30 at Fz were evaluated. Latency indicated speed of the subcortical and cortical somatosensory processing, while amplitude reflected the strength of neural activity. Blood flow in the internal and common carotid arteries (ICA and CCA, respectively) and psychological comfort were recorded in each session. Increases in esophageal temperature due to HS significantly decreased the amplitude of N60, psychological comfort, and ICA blood flow in the HS session, and also shortened the latencies of SEPs (all, $p<0.05$). While esophageal temperature remained elevated, FHC recovered the peak amplitude of N60, psychological comfort, and ICA blood flow toward pre-heat baseline levels as well as WBC. However, the latencies of SEPs did not recover in the FHC and WBC sessions. These results suggest that impaired neural activity in cortical somatosensory processing during passive HS was

recovered by FHC, whereas conduction velocity in the ascending somatosensory input was accelerated by increases in body temperature.

Key Words: Hyperthermia; Somatosensory evoked potentials (SEPs); Conduction velocity; central fatigue; tactile

Introduction

Spontaneous maximal muscle contraction or maximal exercise endurance decreases during severe heat stress (HS) (i.e., when the internal temperature increases by more than 1.5 °C) (5, 17, 19), which is termed 'hyperthermia-induced fatigue', resulting from impairments in psychological and physiological factors in the central nervous system (27). Descending central driving and ascending central processing are altered by HS (24, 25).

Somatosensory-evoked potentials (SEPs), obtained by time-locked averaging electroencephalography (EEG) with high temporal resolution, have been used to evaluate cortical and subcortical somatosensory processing. SEPs are elicited by stimulating peripheral nerves, such as the median nerve at the wrist or posterior tibial nerve at the ankle. When the median nerve is stimulated, the latencies and amplitudes of the P14, N20, P25, N35, P45, and N60 components are recorded at centro-parietal electrodes contralateral to the stimulated site. N20 is the primary response from Brodmann's area 3b of the primary somatosensory cortex, and subsequent components recorded at approximately 20-60 ms are generated in areas 3b, 1, and 4 (1, 2, 13). The P14 component is recorded just before N20, and is generated from higher segments of the cervical cord (31) and at or near the foramen magnum (10). The P22 and N30 components are recorded at the frontal electrodes, and are generated from the primary motor cortex, premotor area, and prefrontal cortex (9, 16, 35).

Our previous study using median nerve stimulation demonstrated that the peak latencies of some SEP components were shortened, but these peak amplitudes were reduced in subjects with increases in body temperature (24). We also reported that the conduction velocity of the ascending somatosensory input was accelerated by increases in body temperature, and aerobic exercise did not alter the strength of neural activity in cortical somatosensory processing (25). However, the mechanisms underlying alterations in ascending central processing due to HS currently remain unknown.

In order to establish a preventable methodology for hyperthermia-induced fatigue, recent studies examined the effects of face cooling during exercise and in a hot environment. They showed that face cooling prolonged workout performance, maintained the prolactin response, and reduced the ratings of perceived exertion and thermal sensation (4, 20, 21, 32, 33). Moreover, maintained cerebral perfusion may be a key factor because cerebral perfusion and oxygenation decrease during prolonged exercise with passive HS (30), resulting in central fatigue. Passive HS decreases cerebral blood flow (6, 11, 28, 38), but increases extra-cranial blood flow (i.e. facial skin blood flow) for heat dissipation (6, 28). Therefore, the recovery of cerebral perfusion due to extra-cranial cooling may contribute to clarifying the mechanisms underlying alterations in ascending central processing during HS. To the best of our knowledge, however, the effects of face/head cooling (FHC) have not yet been investigated on cerebral perfusion. Alternatively, increases in the internal

temperature have been shown to alter ascending central processing. Based on these findings, the aim of the present study was to examine the effects of FHC and whole body cooling (WBC) during passive HS using psychological, physiological, and neuroscientific methods. We utilized SEPs as an index of neural activity in somatosensory (ascending) processing, and hypothesized that neural activity recovers during FHC and/or WBC with improvements in psychological comfort and cerebral perfusion.

Methods

Subjects

Fourteen male subjects (mean age 21.1 years, range 20-24) participated in this study. None of subjects had a history of a neurological or psychiatric disorder. The procedures used complied with the Declaration 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 at the laboratory, subjects weighed themselves nude on a scale, and then only wore 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 in order to measure esophageal temperature. External canal temperature was measured using an infrared sensor (Nipro CE Thermo, NIPRO, Japan), which was insulated with cotton and covered by cling film. Esophageal and external canal temperatures were continuously measured and sampled at 20 Hz via a data acquisition system (MP150, BIOPAC Systems, Santa Barbara, CA, USA). Skin temperatures were measured at six sites (the chest, abdomen, upper and lower back, thigh, and calf). Skin temperatures were also continuously measured using thermocouples, but sampled at 1-sec intervals via another data acquisition system (DA100, YOKOGAWA, Tokyo, Japan). Mean skin temperatures were calculated from the weighted average of six points (34).

Following instrumentation, subjects rested quietly in a semi-supine position on a hospital bed for ~30 minutes. Thermoneutral conditions were maintained by perfusing 33 °C water through a tube-lined suit (Med-Eng, Ottawa, Ontario, Canada), which covered the entire body, except for the head, face, hands, and feet. During this equilibrium period, EEG electrodes were placed on the scalp and earlobes, while other instruments were attached during the equilibration period. Subjects were also instructed on how to use the visual analogue scale (VAS) to score psychological comfort. Scores ranged between -100 mm (uncomfortable) and 100 mm (very comfortable), with a score of 0 mm indicating neutrality. The baseline data of SEPs were recorded (i.e. 1st (Rest) session).

Subjects were then exposed to HS by perfusing 50 °C water through the suit, and the 2nd SEP was recorded after esophageal temperature increased by ~1.2 °C from the pre-HS baseline (HS session). After recording, subjects' faces were thermally cooled using a fan (~0.5 m from their face) (F-CN3X, wind speed: 270 m/min; air volume: 16 m^3/min, TOSHIBA, Tokyo, Japan), and an ice pack was attached to their occipital region. Twelve minutes after this cooling, the 3rd SEP was recorded (FHC session). In this session, we wanted to perform FHC for ten minutes. We needed to confirm that electrode impedance was maintained at less than 5 kohm. If this was not the case, we replaced the electrode using a treatment with alcohol. Therefore, we started the 3rd SEP recording as the FHC session after twelve minutes. During the FHC session, water temperature was regulated to maintain the internal temperature. Cold water (25°C) was then immediately perfused through the suit to decrease mean skin temperatures. When the esophageal temperature was 0.5°C higher than the pre-heat stress baseline, the 4th SEP was recorded (WBC session). Face/head cooling did not continue during WBC (Figure 1).

In order 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 (22-24). The stimulus duration was 0.2 ms, and 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 fixation point positioned in front of them at a distance of approximately 1.5 m. Two hundred stimuli were applied in each session, and the length of the

recording time was approximately 80 sec in each session. The starting time of the session was 63.0 ± 9.8 (SD) min in HS, 76.5 ± 10.1 min in FHC, and 93.4 ± 10.4 min in WBC.

Hemodynamic and thermoregulatory variables

Heart rate was obtained from an electrocardiogram (Biomulti 1000, NEC, Tokyo, Japan) and intermittent arterial blood pressure by auscultation of the brachial artery via electrosphygmomanometry (STBP-780, Colin, Tokyo, Japan) before and after each SEP recording. Skin blood flux was measured via laser-Doppler flowmetry (moor VMS-LDF2, Moor Instruments, UK) using a combined temperature and 8 collecting fibers-bundled probe (VP1T/7, Moor Instruments, UK) attached to the forehead and left forearm. Heart rate, skin blood flux, and local skin temperatures at the forehead and forearm were continuously measured and sampled at 20 Hz via a data acquisition system (MP150, BIOPAC Systems, Santa Barbara, CA, USA). Blood flow was measured in the left ICA and common carotid artery (CCA) using a color-coded ultrasound system (Vivid-i; GE Healthcare, Tokyo, Japan) equipped with a 10-MHz linear transducer. ICA and CCA blood flow measurements were performed ~1.0-1.5 cm distal and proximal to the carotid bifurcation, respectively. Blood flow was measured 1 min before each session. The diameter of each vessel was measured at three points in a longitudinal section using the brightness mode, and the Doppler velocity spectrum was subsequently identified using the pulsed wave mode. Systolic and diastolic diameters

were measured in detail, and the mean diameter (cm) was then calculated in relation to the blood pressure curve: mean diameter = [(systolic diameter × 1/3)] + [(diastolic diameter × 2/3)]. The time-averaged mean flow velocity obtained in the pulsed wave mode was defined as the mean blood flow velocity (cm/s). Blood flow velocity was measured from the average of ~10-20 cardiac cycles in order to eliminate the effects of the breathing cycle. When making blood flow velocity measurements, care was taken to ensure that the probe position was stable, that the insonation angle did not vary (~60 deg in most cases), and that the sample volume was positioned in the center of the vessel and adjusted to cover the width of the vessel diameter. Blood flow was calculated by multiplying the cross-sectional area [π × (mean diameter/2)2] by mean blood flow velocity; Blood flow = mean blood flow velocity × area × 60 (ml min−1). ECA blood flow was estimated by subtracting blood flow in the ICA from that in the CCA. The same operator performed all blood flow measurements.

EEG recordings

SEPs were recorded using 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 (Figure 2). 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 neural activities generated by the primary motor cortex, premotor area, and prefrontal cortex. The Cz and

Pz electrodes were supplementarily used in order to assess the peak amplitudes and latencies of each component at C4' and Fz. Each electrode was referenced to linked earlobes. In order to eliminate 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. Impedance was maintained at less than 5 kohm and was measured before SEP recording for each session. All EEG signals were collected on a signal processor (Neuropack MEB-2200 system, Nihon-Kohden, Tokyo, Japan). The bandpass filter of the amplifier was 1-1500 Hz. The analysis time was 100 ms including a prestimulus baseline period of 10 ms for P14 at C4' and P14 at Fz. The sampling rate was 5000Hz. The peak amplitude for P14 was measured using baseline-to-peak as the far-field potential. Regarding subsequent components (i.e., N20, P25, N35, P45, and N60 at C4', and N18, P22, and N30 at Fz), the peak-to-peak measurement was used because the sequential component may be affected by the previous component. For example, the amplitude of N35 is easily affected by the amplitude of P25, and N35 often shows a positive rather than negative potential when the baseline-to-peak measurement is used. We employed the same analysis methods as those reported previously (12, 22-24, 37). The peak amplitudes and latencies for the individual SEP components were assessed using a measuring scale on the Neuropack system with visual inspection.

Data analyses

A 60-sec 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 and hemodynamic variables were analyzed by a one-way analysis of variance (ANOVA) with repeated measures using the within-subject factor of Session (Rest, HS, FHC, and WBC). 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). Based on previous studies, we focused on the C4' and Fz electrodes (22-24). Peak latencies at C4' were identified in the P14, N20, P25, N35, P45, and N60 components, and peak amplitudes were measured for N20 (P14-N20), P25 (N20-P25), N35 (P25-N35), P45 (N35-P45), and N60 (P45-N60). Peak latencies at Fz were identified in the 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 one-way ANOVA with Session as a factor. 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. When the significant effects of Session were identified, the post-hoc paired *t*-test was adjusted to identify specific differences between Rest (the 1st) and other sessions. Statistical tests

were performed using computer software (SPSS for windows ver. 22.0, SPSS). Significance was set at $p < 0.05$.

Results

Temperature, hemodynamic, and skin blood velocity variables are listed in Table 1.

Temperature variables

ANOVAs for mean skin temperatures, esophageal temperature, and external canal temperature showed the significant main effects of Session (Greenhouse-Geisser correction: $F (1.808, 21.696) = 295.552$, $p < 0.001$, $\varepsilon = 0.603$; $F (3, 39) = 375.685$, $p < 0.001$; Greenhouse-Geisser correction: $F (1.488, 17.856) = 21.453$, $p < 0.001$, $\varepsilon = 0.496$). ANOVAs for local skin temperatures at the forehead and forearm also revealed the significant main effects of Session ($F (3, 36) = 47.102$, $p < 0.001$; Greenhouse-Geisser correction: $F (1.334, 16.009) = 40.302$, $p < 0.001$, $\varepsilon = 0.445$). Esophageal and external canal temperatures were maintained with FHC. In the WBC session (4th session), skin temperatures at the forehead and forearm decreased, indicating that they had returned to the pre-heating level with WBC.

322 *Hemodynamic variables*

323 ANOVAs for heart rate showed the significant main effect of Session (3,
324 36) = 331.253, $p < 0.001$). Heart rate increased with HS, and was
325 maintained with FHC. Heart rate with WBC almost returned to the
326 pre-heating level, but was still significantly higher than that at Rest.
327 ANOVAs for mean blood pressure also showed the significant main effect
328 of Session (3, 30) = 6.137, $p < 0.01$), whereas the post-hoc test did not
329 detect any significant differences between Rest and the other sessions.
330 ANOVAs for skin blood flux at the forehead and forearm demonstrated
331 the significant main effects of Session (3, 36) = 26.771, $p < 0.001$;
332 Greenhouse-Geisser correction: $F (1.695, 18.640) = 26.864$, $p < 0.001$, $\varepsilon =$
333 0.565). The post-hoc test revealed that skin blood flux at the forehead and
334 forearm was significantly larger with HS than at Rest. In the FHC session,
335 skin blood flux at the forehead decreased, but was significantly larger with
336 FHC than at Rest. Skin blood flux at the forearm was also significantly
337 larger with FHC than at Rest. In the WBC session, skin blood flux at the
338 forehead returned to the pre-heating level, whereas that at the forearm was
339 still significantly smaller than that at Rest.
340
341 *Blood flow variables*
342 Figures 3A, 3B, and 3C show the mean values of ICA, CCA, and ECA
343 with SD, respectively. ANOVAs for ICA, CCA, and ECA demonstrated
344 the significant main effects of Session (Greenhouse-Geisser correction: F
345 $(1.542, 13.877) = 5.568$, $p < 0.05$, $\varepsilon = 0.514$; $F (3, 24) = 37.892$, $p < 0.001$;

346 F (3, 24) = 36.194, $p < 0.001$).

347 ICA blood flow was significantly lower with HS than at Rest ($p < 0.001$),
348 whereas blood flow in the CCA and ECA was significantly higher with HS
349 than at Rest ($p < 0.001$, respectively). In the FHC session, blood flow in
350 the ECA was lower with FHC than with HS, while that in the ICA returned
351 to the pre-heat level ($p > 0.05$). No significant differences were observed
352 in blood flow in the ICA, CCA, and ECA between at Rest and with WBC.

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354 *VAS for psychological comfort*

355 Figure 3D shows VAS with SD, with the significant main effect of
356 Session being observed (F (3, 39) = 49.975, $p < 0.001$). Post-hoc tests
357 demonstrated that psychological comfort was significantly lower with HS
358 than at Rest ($p < 0.001$), and was higher with WBC than at Rest ($p <$
359 0.001).

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361 *Peak latency of SEPs*

362 Figure 4 shows grand-averaged SEP waveforms at C4' for each session,
363 and the P14, N20, P25, N35, P45, and N60 components were examined.
364 Figure 5 shows the grand-averaged SEP waveforms at Fz for each session,
365 and the P14, N18, P22, and N30 components were assessed.

366 ANOVAs for the peak latency of P14, N20, P25, and N35 at C4' showed
367 the significant main effect of Session (F (3, 39) = 17.197, $p < 0.001$; F (3,
368 39) = 26.078, $p < 0.001$; F (3, 39) = 3.461, $p < 0.05$; (F (3, 39) = 4.433, $p <$
369 0.01). The post-hoc test showed that these peak latencies were

significantly shorter with HS and FHC than at Rest. Moreover, latencies were significantly shorter with WBC than at Rest (Table 2). ANOVAs for the peak latencies of P14, N18, and P22 at Fz showed the significant main effect of Session ($F(3, 39) = 7.047$, $p < 0.01$; $F(3, 39) = 4.385$, $p < 0.01$; $F(3, 39) = 6.514$, $p < 0.01$). The post-hoc test also showed that these peak latencies were significantly shorter with HS, FHC, and WBC than at Rest (Table 2).

There were no significant main effects in the peak latencies of P45 or N60 at C4' or N30 at Fz.

Peak amplitude of SEPs

ANOVAs for the peak amplitude of N60 at C4' showed the significant main effect of Session ($F(3, 39) = 3.056$, $p < 0.05$). The post-hoc test indicated that the peak amplitude of N60 was significantly smaller with HS than at Rest ($p < 0.01$). There were no significant main effects in the peak amplitudes of N20, P25, N35, or P45 at C4' or N18, P22, or N30 at Fz (Table 3).

Discussion

We herein demonstrated the effects of FHC and WBC during passive HS on human somatosensory processing using SEPs. The peak latencies of some SEP components were significantly shortened by increases in body

temperature and this acceleration was maintained during FHC. In addition, latency was still accelerated during WBC. On the other hand, the peak amplitude of N60 at C4' decreased with increases in body temperature, but recovered with FHC and WBC.

Effects of HS

The peak latencies of P14, N20, P25, and N35 at C4', and P14, N18, and P22 at Fz were shortened with increases in body temperature in the HS session (Figures 4 and 5, and Table 2), which was consistent with our previous findings (24). The primary response of SEPs was recorded approximately 20 ms after stimulating the median nerve, and was referred to as the N20 component. As described in the Introduction section, 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. Thus, our results indicated that the conduction velocity of the ascending somatosensory input was accelerated by increases in body temperature. The P14 component, which is recorded just before N20, is generated from higher segments of the cervical cord (31) and at or near the foramen magnum (10). P14 at C4' and Fz was accelerated in the HS session, indicating acceleration not only in cortical processing, but also in subcortical processing. In addition, the peak latencies of P25 and N35 were significantly shorter with HS than at Rest. The generator mechanisms for P25 and N35 remain unknown.

418 A previous study using dipole modeling with magnetoencephalography
419 identified multiple cortical areas as generators at approximately 20-60 ms,
420 involving areas 3b, 1, and 4 and the posterior parietal cortex (13). The
421 P25 component is also known to reflect different neural processing from
422 the N20 component. N20 is generated from area 3b of the primary
423 somatosensory cortex, whereas P25 is generated from area 1 (3, 13). In
424 contrast, Valeriani and colleagues (36), using brain electrical source
425 analysis, showed a common generator for the N20 and P24 components,
426 which may represent the opposite counterparts of the primary response.
427 P25 and N35 has been suggested to arise not only from the primary
428 somatosensory cortex (area 1), but also from more anterior areas including
429 area 4 (15, 18).

430 The peak amplitudes of N60 were significantly smaller in the HS session
431 than in the Rest session (Figure 4, and Table 2), which was consistent with
432 our previous findings (24). N60 and other SEP components including
433 N20, P25, N35, and P45 are known to be generated from the primary
434 somatosensory cortex. However, Barba and colleagues (7, 8), utilizing
435 depth electrodes on epilepsy patients, reported that the fronto-central N60
436 response originated from not only the primary somatosensory cortex, but
437 also the supplementary motor area. Based on these findings, neural
438 activities including those at the primary somatosensory cortex and
439 supplementary motor area became impaired with HS.

440 Blood flow in the CCA and ECA increased with HS, whereas ICA blood
441 flow was less with HS than at Rest, which was also consistent with

previous findings (Figure 3) (28). This result indicated that HS modified the distribution of intra- and extracranial blood flow.

Effects of FHC

In the FHC session, the values for peak latencies during FHC were similar to those during HS, indicating that peak latencies remained accelerated even during FHC. In other words, FHC did not affect the conduction velocity of ascending signals from the periphery to the subcortical regions and primary somatosensory cortex (Figures 4 and 5, and Table 2).

On the other hand, the peak amplitude of N60 was recovered by FHC in the FHC session (Figure 4, and Table 3). Since N60 is the latest component among these SEP components, the neural mechanisms involved may be more complex and higher than other earlier SEP components. For example, N60 was more easily affected by various somatosensory inputs than the other SEP components during passive HS (24), movement preparation (14), and mastication (26).

The present study attempted to clarify whether FHC recovered ICA and ECA to pre-baseline levels. Consistent with our hypothesis, FHC recovered cerebral perfusion (Figure 3). In addition, psychological comfort was also recovered by FHC (Figure 3D). As for modulations of the peak amplitude of N60, cerebral perfusion and psychological comfort may be related to the strength of neural activity in somatosensory processing. An adequate supply of oxygen and glucose is needed for

adequate brain functions. We assumed that the recovery of cerebral blood flow contributes to variations in the changes observed in the amplitude of SEPs.

Although the impedance of each electrode was verified for each session, changes in the sweat rate during the recording may affect the amplitude of SEP components. However, HS and FHC only affected the amplitude of N60 at C4'. Other SEP components at C4' and Fz did not change throughout the experiment. Therefore, the reduction observed in the amplitude of N60 to HS was unlikely to be affected by sweat-induced shifts in potential.

Effects of WBC

In the WBC session, the peak amplitude of N60 recovered to the pre-heat level observed in the Rest session (Figures 4 and 5, and Table 3). The results obtained for temperature variables in the WBC session also showed that body temperature and cerebral perfusion recovered to those in the Rest session (Figure 3). However, the peak latencies of P14, N20, and P25 at C4' and P14 and N22 at Fz were still significantly earlier in the WBC session than in the Rest session (Figures 4 and 5, Table 2). These results suggest the after effects of passive HS; even if body temperature, psychological comfort, and cerebral perfusion have sufficiently recovered to pre-heat stress levels, ascending somatosensory processing is still affected. In other words, abnormal ascending signals may still remain at this time. However, we did not examine how long this after effect on the

peak latency of SEPs existed. Therefore, further studies are needed to clarify this issue.

Limitations of the present study

Although we showed reductions and the recovery of the peak amplitude of N60 by utilizing SEPs during passive HS and FHC, it currently remains unknown whether higher cognitive functions or neural activities for other sensory modalities such as auditory and visual processing are also modulated, similar to our previous findings, because we only focused on neural activity in ascending somatosensory processing. Moreover, the present study did not directly evaluate the actual perception and cognition of the somatosensory stimulus using psychophysical tests. We examined modulations in the peak amplitude and latency of some SEP components during each session. The relationship between modulations in SEPs and actual cognitive performance need to be clarified in future studies.

Perspectives and Significance

The present study using SEPs showed the effects of FHC during passive HS on psychological comfort, cerebral perfusion, and human somatosensory processing. The results obtained appear to provide insights into the psychological, physiological, and neuroscientific mechanisms underlying hyperthermia. Our results may contribute to the development of a preventative methodology for hyperthermia in daily life and sports activities. In recent decades, a number of severe heat waves

514 have occurred throughout the Northern Hemisphere (29). FHC may be
515 one of the simple and effective methods for maintaining psychological
516 comfort, cerebral perfusion, and the somatosensory system during
517 hyperthermia. In future studies, other preventative methodologies, such
518 as drinking, an effective cooling time period, and cooling of other body
519 parts, need to be established.
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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions

H.N., R.K., and M.S. conception and design of the research; H.N., M.N., and M.S. performed experiments; H.N, and M.S. analyzed the data; H.N. and M.S. interpreted the results of the experiments; H.N. prepared figures; H.N., R.K., and M.S. drafted the manuscript.

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706 **Figure Legends**

707

708 **Figure 1:** Schema of the experimental time course. CBF = recording for
709 cerebral blood flow; Tes = esophageal temperature

710

711 **Figure 2:** Electrode placement used in the present study. Cz is located
712 midway between the nasion and inion, and between the bilateral
713 pre-auricular points. C4' was 2 cm posterior to C4. LRA = left
714 pre-auricular; RPA = right pre-auricular

715

716 **Figure 3:** Blood flows and thermal comfort. (A) ANOVAs for internal
717 carotid artery (ICA) blood flow demonstrated the significant main effects
718 of Session, and post-hoc test showed that ICA blood flow was significantly
719 lower with HS (2nd session) than at Rest (1st session) ($p < 0.001$). (B)
720 ANOVAs for common carotid artery (CCA) blood flow demonstrated the
721 significant main effects of Session, and a post-hoc test showed that CCA
722 blood flow was significantly higher with HS and FHC (3rd session) than at
723 Rest ($p < 0.001$ and $p < 0.01$, respectively). (C) ANOVAs for external
724 carotid artery (ECA) blood flow demonstrated the significant main effects
725 of Session, and a post-hoc test showed that ECA blood flow was
726 significantly higher with HS and FHC than at Rest ($p < 0.001$, and $p < 0.01$,
727 respectively). (D) Psychological comfort in the visual analogue scale was
728 significantly smaller with HS than at Rest ($p < 0.001$), but was restored by
729 FHC, while subjects felt comfortable with WBC (4th session) ($p < 0.001$).

730 Values are the mean ± standard deviation. **: $p < 0.01$; ***: $p < 0.001$

731

732 **Figure 4:** Grand-averaged SEP waveforms in the experimental session at
733 C4' across all subjects (n = 14). Black lines indicate waveforms at Rest,
734 and gray lines show waveforms with HS, FHC, and WBC. Asterisks (*)
735 show components with peak latencies that were significantly shorter than
736 those at Rest. Sharps (#) show components with peak amplitudes that
737 were significantly smaller than those at Rest.

738

739 **Figure 5:** Grand-averaged SEP waveforms in the experimental session at
740 Fz across all subjects (n = 14). Black lines indicate waveforms at Rest,
741 and gray lines show waveforms with HS, FHC, and WBC. Asterisks (*)
742 show components with peak latencies that were significantly shorter than
743 those at Rest. No significant differences were observed in the amplitude
744 of any component between any session.

745

746

747

Table 1: Temperature, hemodynamic, and skin blood velocity variables (n = 14).

	Rest (1st session)	HS (2nd session)	FHC (3rd session)	WBC (4th session)
Tes, °C	36.8 (0.2)	38.1 (0.2) ***	37.9 (0.2) ***	37.0 (0.2) **
Tear, °C	36.9 (0.3)	38.2 (0.3) ***	37.6 (0.6) *	36.6 (0.6)
Tsk, °C	34.2 (0.7)	39.1 (0.6) ***	38.7 (0.5) ***	34.0 (0.9)
Local skin temperature, °C				
Forehead	32.7 (1.1)	34.6 (0.8) ***	31.0 (0.8) ***	32.3 (1.4)
Forearm	33.1 (0.6)	37.2 (1.6) ***	37.0 (1.4) ***	32.9 (1.7)
Skin blood flux, au				
Forehead	43.4 (12.2)	135.1 (49.3) ***	122.2 (38.9) ***	69.6 (49.2)
Forearm	17.5 (14.4)	76.1 (29.3)***	72.9 (24.5) ***	39.8 (21.4) *
HR, bpm	64.4 (9.0)	107.4 (13.5) ***	103.3 (11.8) ***	70.9 (11.8) **
MAP, mmHg	91.8 (8.3)	88.2 (6.9)	86.9 (6.9)	95.6 (9.0)

Data were expressed as the mean (SD). Post-hoc results vs. Rest * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$
Tes = esophageal temperature; Tear = external canal temperature; Tsk = mean skin temperature; HR = heart rate; MAP = mean arterial blood pressure

Table 2: Peak latencies (ms) of somatosensory evoked potentials and statistical results at C4' and Fz (n = 14).

		Rest (1st session)	HS (2nd session)	FHC (3rd session)	WBC (4th session)
C4'	P14	14.6 (0.2)	13.1 (0.2)***	13.5 (0.2)***	14.2 (0.2)*
	N20	19.4 (0.2)	18.1 (0.1)***	18.0 (0.2)***	18.9 (0.1)*
	P25	24.2 (0.2)	23.1 (0.4)*	23.3 (0.3)	23.3 (0.3)*
	N35	30.5 (0.8)	29.0 (0.7)*	29.9 (0.8)	30.7 (0.7)
	P45	42.7 (1.1)	41.9 (0.9)	42.1 (1.1)	43.4 (0.9)
	N60	57.8 (0.8)	56.8 (0.9)	57.4 (1.1)	58.1 (1.0)
Fz	P14	14.4 (0.2)	12.9 (0.3)**	13.5 (0.2)**	13.6 (0.2)*
	N18	16.7 (0.3)	16.0 (0.2)*	16.2 (0.2)*	16.4 (0.2)
	P22	19.2 (0.2)	18.6 (0.2)**	18.7 (0.2)*	18.8 (0.2)*
	N30	29.9 (0.9)	28.7 (0.8)	29.3 (0.8)	29.2 (0.8)

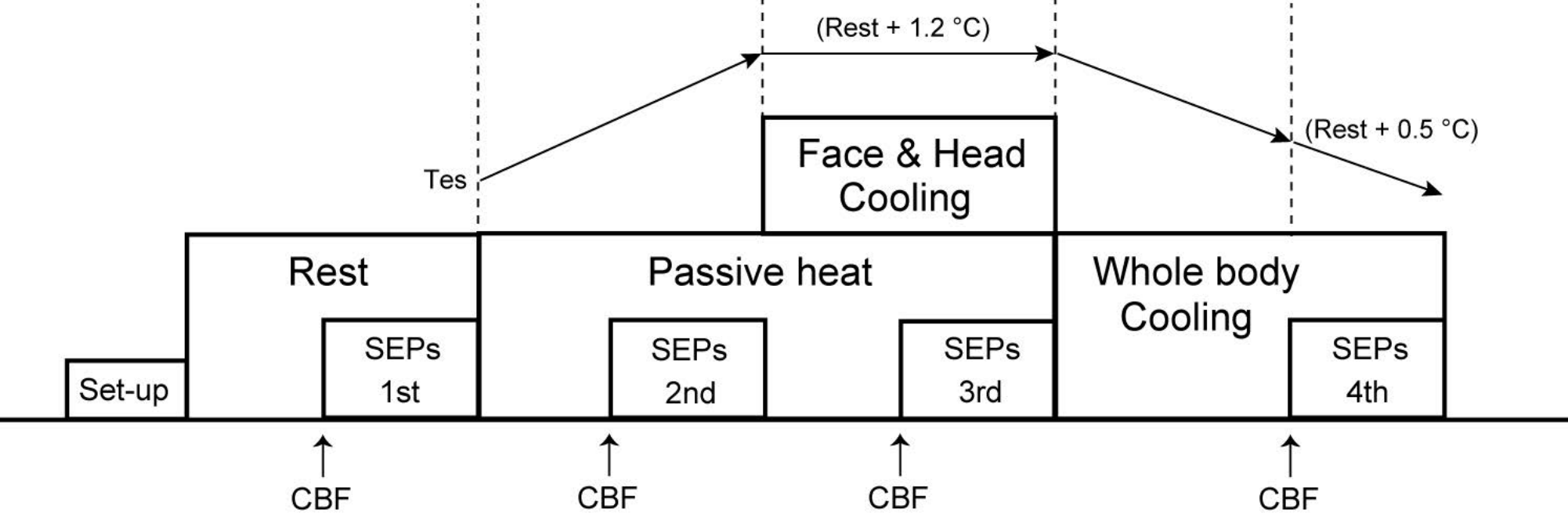
Data were expressed as the mean (SE). Post-hoc results vs. Rest * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$

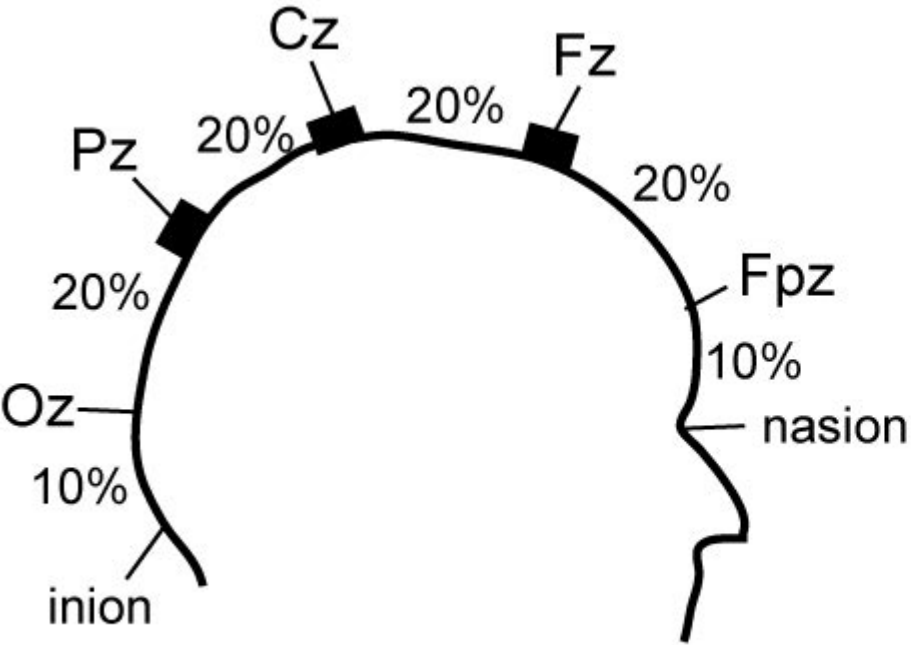
771 **Table 3:** Peak amplitudes (μV) of somatosensory evoked potentials and statistical results at C4' and Fz (n = 14).
772

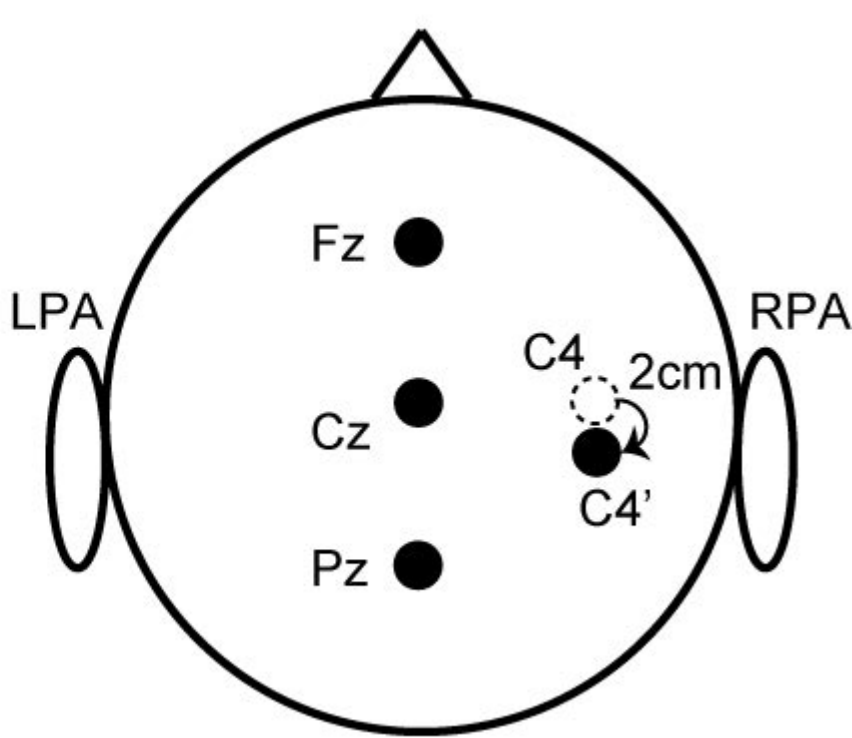
		Rest (1st session)	HS (2nd session)	FHC (3rd session)	WBC (4th session)
C4'	N20	2.7 (0.3)	2.6 (0.2)	2.5 (0.2)	2.5 (0.3)
	P25	3.4 (0.4)	3.2 (0.4)	3.3 (0.4)	3.5 (0.4)
	N35	2.0 (0.3)	2.1 (0.3)	2.2 (0.3)	2.3 (0.3)
	P45	3.3 (0.3)	3.2 (0.3)	3.4 (0.4)	3.4 (0.3)
	N60	4.5 (0.4)	3.4 (0.5)**	4.1 (0.7)	4.1 (0.5)
Fz	N18	1.2 (0.1)	1.3 (0.1)	1.6 (0.2)	1.3 (0.1)
	P22	1.2 (0.1)	1.3 (0.1)	1.5 (0.2)	1.3 (0.1)
	N30	3.3 (0.4)	3.0 (0.3)	3.1 (0.4)	3.5 (0.4)

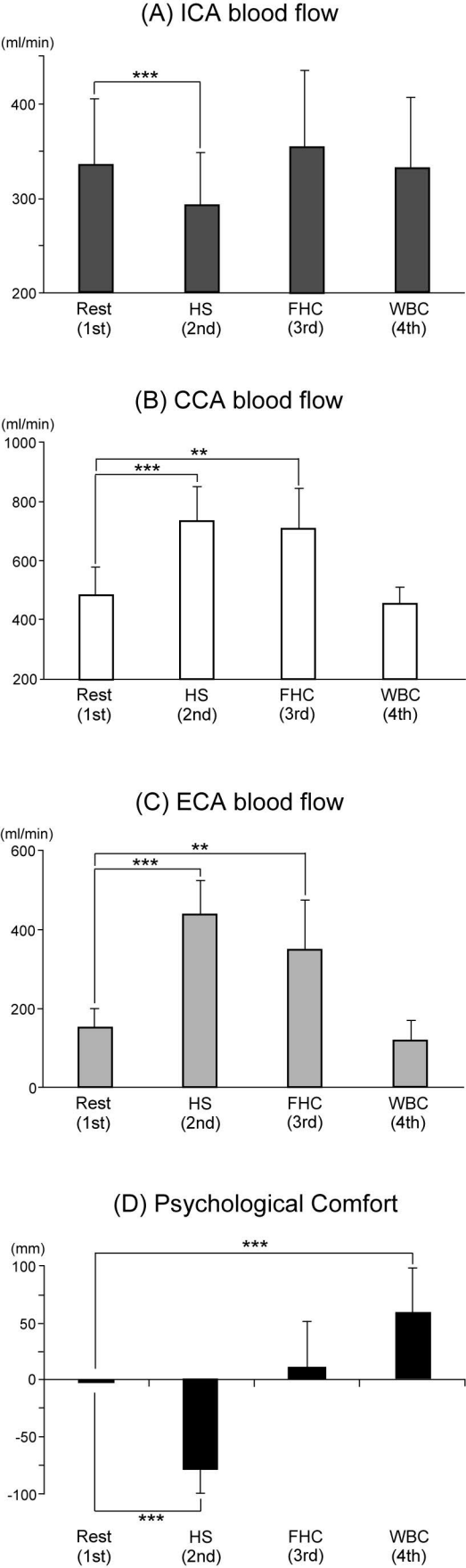
773

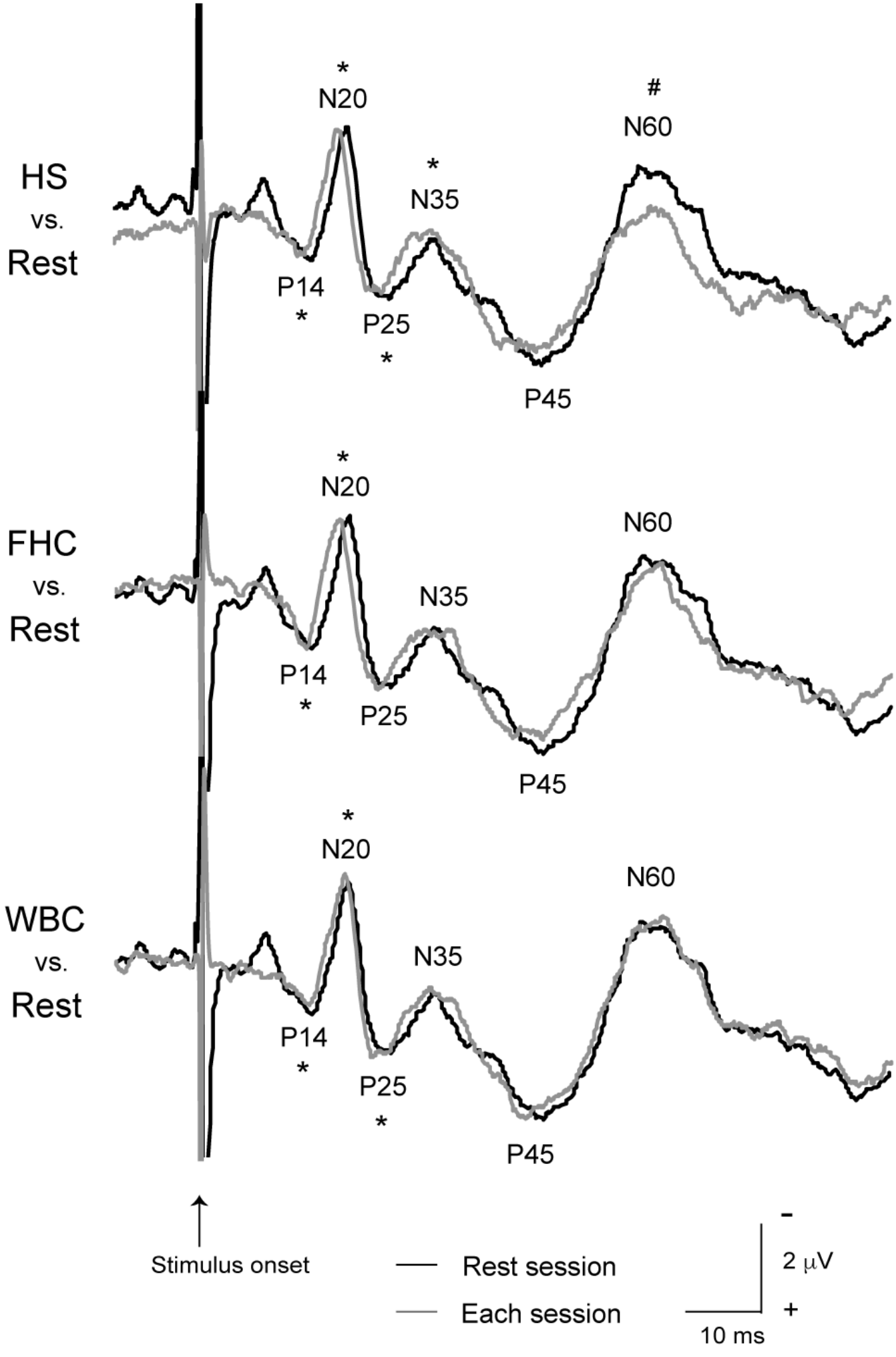
774 Data were expressed as the mean (SE). Post-hoc results vs. Rest ** $p < 0.01$

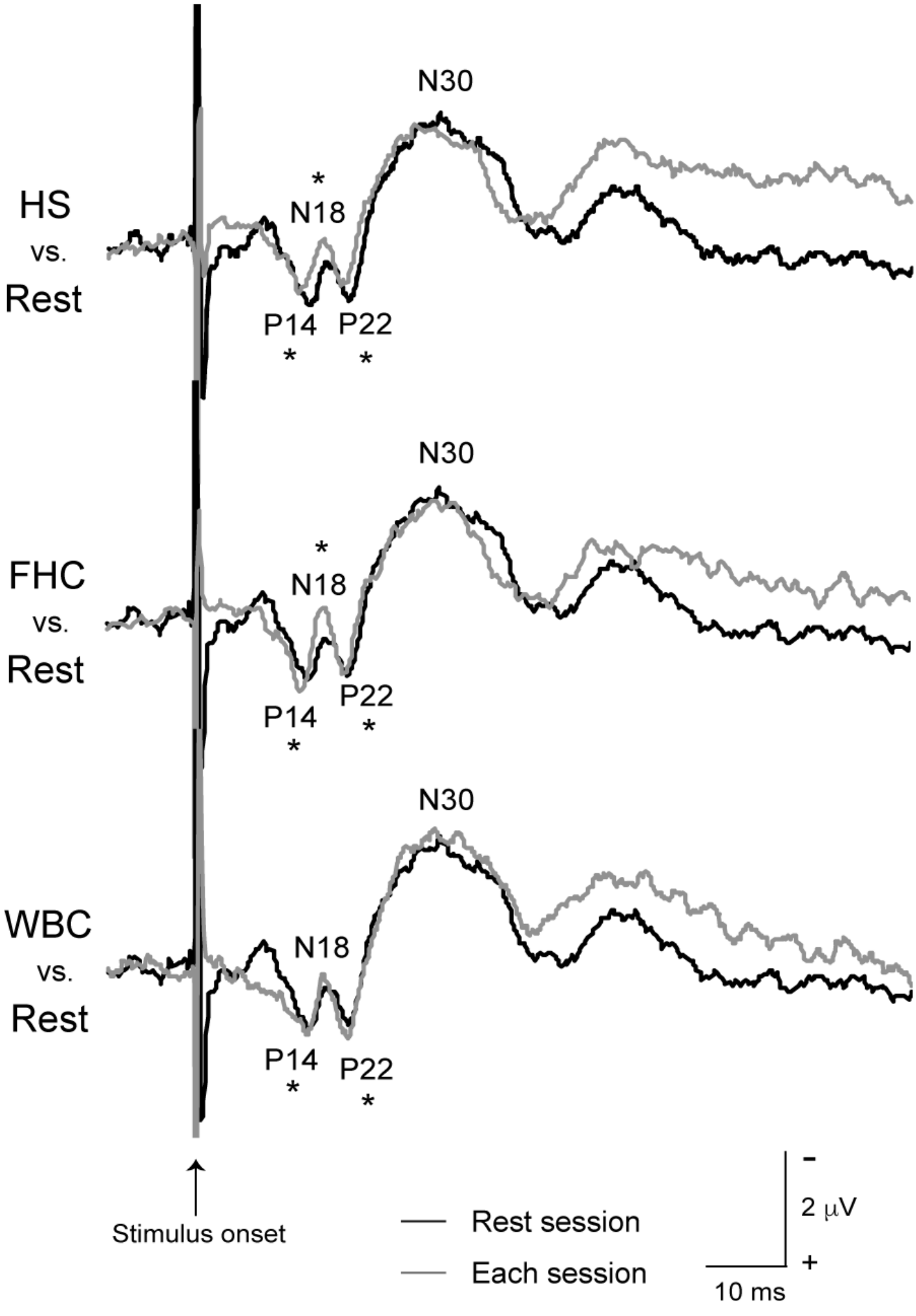

(Rest + 1.2 °C)
(Rest + 0.5 °C)
Tes
Face & Head Cooling
Rest
Passive heat
Whole body Cooling
Set-up
SEPs 1st
SEPs 2nd
SEPs 3rd
SEPs 4th
CBF
CBF
CBF
CBF


Cz
Fz
Pz
20%
20%
20%
20%
Fpz
10%
nasion
Oz
10%
inion


Fz
LPA
RPA
C4
2cm
Cz
C4'
Pz


(A) ICA blood flow
(ml/min)
400
300
200
***
Rest (1st)
HS (2nd)
FHC (3rd)
WBC (4th)
(B) CCA blood flow
(ml/min)
1000
800
600
400
200
**
***
Rest (1st)
HS (2nd)
FHC (3rd)
WBC (4th)
(C) ECA blood flow
(ml/min)
600
400
200
0
**
***
Rest (1st)
HS (2nd)
FHC (3rd)
WBC (4th)
(D) Psychological Comfort
(mm)
100
50
0
-50
-100
***
***
Rest (1st)
HS (2nd)
FHC (3rd)
WBC (4th)


HS
vs.
Rest
*
N20
*
N35
#
N60
P14
*
P25
*
P45
FHC
vs.
Rest
*
N20
N60
N35
P14
*
P25
P45
WBC
vs.
Rest
*
N20
N60
N35
P14
*
P25
*
P45
Stimulus onset
Rest session
Each session
-
2 μV
+
10 ms


HS
vs.
Rest
N30
N18
P14
P22
FHC
vs.
Rest
N30
N18
P14
P22
WBC
vs.
Rest
N30
N18
P14
P22
Stimulus onset
Rest session
Each session
2 μV
10 ms