High internal temperature, ranging from 38.6 to 40.3°C, is associated with voluntary exhaustion during aerobic exercise, despite variations in baseline core temperature, heat storage rates, and final skin temperature (4, 10). Similarly, hyperthermia has been shown to produce motor fatigue, evidenced by decreased voluntary activation during sustained maximal voluntary contractions (MVC) (16, 34). Cardiovascular strain during thermal stress contributes to the development of fatigue; however, evidence also suggests that hyperthermia alters central nervous system (CNS) functions, resulting in alterations in voluntary activation of muscle, as well as changes in perception of effort (18, 24, 33). Little is known about the effects of moderate core temperature increases, in the range between 0.5 to 1.0°C, on CNS function in healthy individuals, although some evidence suggests that decrements in function may begin to appear when core temperatures exceed normal levels (18, 24, 33).

Individuals with multiple sclerosis (MS), a demyelinating disease of the CNS, commonly experience fatigue that is exacerbated by relatively small (0.5°C) increases in core temperature (11). It has been hypothesized that heat-related fatigue in MS is a form of central fatigue, produced by conduction slowing and/or block in areas of demyelination in the corticospinal system (11, 29). It would therefore be expected that thermal stress would produce increases in fatigue perception and exaggerated decrements in task performance in MS patients compared with healthy individuals. However, experimental support for this hypothesis is derived from studies of demyelinated peripheral nerve (11, 22).

Transcranial magnetic stimulation (TMS) is a noninvasive technique that has been used to study conduction properties of the corticospinal tract and excitability of the motor cortex, as well as CNS changes in response to thermal stress. Comparing motor-evoked potential amplitude (MEPamp) before and after fatigue activation, as one method used to examine central fatigue (5). Postexercise depression (PED), a generalized decrease of MEPamp following fatigue exercise, has been demonstrated in healthy individuals (1, 2, 13, 28) and MS patients (14, 21) but has not been examined with respect to thermal stress. Cortical excitability can be examined through analysis of the recruitment curve, in which MEPamp are assessed relative to increases in stimulation intensity. The slope of this recruitment curve is a function of cortical excitability (24). Additionally, assessment of changes in the cortical silent period (SP), the interruption of ongoing EMG activity induced by motor cortex stimulation, may indicate altered inhibitory activity to corticospinal neurons (31). Therefore, the primary aim of the present investigation was to test the hypothesis that passive heat exposure in MS patients will lead to increased subjective fatigue and impairments in physiological measures of central conduction and cortical excitability compared with healthy individuals.

METHODS

Subjects

Eleven healthy individuals and 11 individuals with definite relapsing-remitting MS (all between 18 and 55 yr of age) were studied (Table 1). All MS patients demonstrated stable disease condition for the 3 mo preceding the study and had no spasticity or hyperreflexia in
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11 (7 F)</td>
<td>11 (7 F)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>37.4 ± 9.6</td>
<td>38.9 ± 6.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5 ± 3.6</td>
<td>27.1 ± 4.9</td>
</tr>
<tr>
<td>Physical activity frequency, days/wk</td>
<td>3.6 ± 2.3</td>
<td>3.8 ± 3.0</td>
</tr>
<tr>
<td>Physical activity duration, min</td>
<td>42 ± 18.6*</td>
<td>24 ± 17.8</td>
</tr>
<tr>
<td>FIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 ± 9.2*</td>
<td>61 ± 39.1</td>
</tr>
<tr>
<td>Cognitive</td>
<td>3.6 ± 3.3*</td>
<td>15.5 ± 12.4</td>
</tr>
<tr>
<td>Physical</td>
<td>2.0 ± 2.3*</td>
<td>17.3 ± 7.5</td>
</tr>
<tr>
<td>Social</td>
<td>4.3 ± 4.2*</td>
<td>27.7 ± 21.2</td>
</tr>
<tr>
<td>Years since MS diagnosis</td>
<td>NA</td>
<td>5.6 ± 2.0</td>
</tr>
<tr>
<td>EDSS</td>
<td>NA</td>
<td>1.9 (1.0–3.0)</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects; MS, multiple sclerosis; F, females; BMI, body mass index; FIS, Fatigue Impact Scale; EDSS, Expanded Disability Status Scale. *Significant difference from MS, P < 0.05. NA, not available.

the upper extremities. Each MS patient was matched to a control for gender, age (within 5 yr), body mass index (BMI, within 3 units), and physical activity (frequency ±1 day/wk and duration ±30 min/session). Physical activity was assessed by interview. All subjects provided written informed consent to participate in the protocol that was approved by the University of Utah Institutional Review Board. MS patients were examined according to the outline of the Minimal Record of Disability for Multiple Sclerosis (30), and patients with an Expanded Disability Status Scale score between one and six, with self-reported fatigue exacerbated by thermal stress participated. The Fatigue Impact Scale (8) was used to assess the overall effect of subjective fatigue, as well as effects on cognitive, physical, and social functions.

Instrumentation

Heart rate was obtained from an electrocardiogram (Biopac System, Santa Barbara, CA). Internal temperature was indexed from an ingestible capsule telemetry system (HTI Technologies, Palmetto, FL). The telemetry pill correlates well with other methods of internal temperature measurement (20). Mean skin temperature was measured via the weighted average of four thermocouples (chest, back, thigh, and calf) taped to the skin.

Measures of Central Conduction and Cortical Excitability

Nerve conduction. Median nerve conduction from elbow to wrist was assessed. Muscle responses were recorded from the abductor pollicis brevis (APB) with 1-cm silver disc electrodes in a belly-bendon montage. EMG responses were displayed using a Synergy (Viasys) EMG system. Sweep speed was set at 5–10 ms/div and amplification set at 5,000 for compound muscle action potential (CMAP) and 500–1,000 for motor-evoked potentials, filtered at a band pass of 10–2,000 Hz. Peak-to-peak CMAP amplitude of APB resulting from supramaximal stimulation at the wrist was determined, as well as distal motor latency. Median nerve conduction velocity was calculated from stimulation at the wrist and elbow. Minimum F-wave latency from 20 trials was recorded for subsequent central motor conduction time (CMCT) calculations.

TMS. A Magstim 200° (Wales, UK) magnetic stimulator and a 70-mm double coil were used for magnetic stimulation. Subjects were tested in a semireclined supine position and were right hand dominant, except for one left-handed control. For each subject, an estimate for the intrinsic hand muscle area in the motor cortex was marked on a snug-fitting swim cap 5 cm lateral to the vertex. Stimuli were centered over this point and in the surrounding region to determine the site at which TMS evoked a maximal motor response in the right APB muscle. With the magnet over this “hot spot,” an outline of the stimulator was traced on the cap to mark the proper position for subsequent TMS studies. Resting motor threshold (RMT) was determined by gradually increasing stimulus intensity, beginning at 50% maximal stimulator output, until a detectable MEP (50 μV) was elicited in 4–6 out of 10 stimuli (3). Baseline MEPs were recorded at 120% RMT from the resting right APB muscle. Right APB muscle activity was monitored to ensure EMG silence during the trials. Fifteen MEPs, recorded at 10-s intervals, were obtained for analysis of CMCT and peak-to-peak MEP\(_{\text{amp}}\). CMCT was calculated as follows (26):

\[
\text{CMCT} = \left[ \text{MEP}_{\text{lat}} - (\text{DML} + \text{FW} - 1)/2 \right]
\]

where MEP\(_{\text{lat}}\) is shortest MEP latency of 15 trials recorded from the APB, DML is distal motor latency determined from supramaximal median nerve stimulation at the wrist, and FW is minimum F-wave latency from 20 trials.

Recruitment curves. MEP recruitment curves were determined from stimulus intensities of 100, 110, 120, and 130% of RMT, as described by Chen et al. in 1998 (3). At each stimulus intensity, 12–15 responses were recorded at 15-s intervals and were subsequently expressed relative to the peak baseline CMAP amplitude obtained during the corresponding thermal condition. Averaged values were used to plot recruitment curves for MS patients and controls during heat stress (HS) and thermoneutral (TN) conditions. Recruitment curve slope was determined in each subject during HS and TN conditions from the steepness of the regression line through the four data points (25).

Cortical SP. Stimulation intensity was increased to 1.5 times RMT and delivered during antigravity preactivation of the right APB muscle, in which subjects were asked to fully abduct the thumb for each of the SP recordings (12). This level of activation was estimated to be ~15–20% of MVC. Fifteen recordings, obtained at 10-s intervals, were averaged for determination of SP duration.

Motor fatigue task. The motor fatigue task, consisting of 3 min of sustained, maximal-effort thumb abduction exercise, followed the baseline TMS studies. Thumb abduction force was measured using a fixed platform containing a force transducer positioned over the thumb and hand, and the forearm and hand were supported in a fixed supinated position. Force data were acquired at 20 Hz and stored to a DataPac data acquisition system for later analysis of peak force and elapsed time to reach 50% force reduction (T\(_{50\%}\)).

PED. Immediately following the motor fatigue task, TMS was applied at 120% RMT at 1, 4, 6, 8, and 10 min postexercise. Sets of eight MEPs, which were later averaged, were obtained at each of these times at an interstimulus time interval of 15 s.

Protocol

Measures of central conduction and cortical excitability were performed during TN and mild whole body HS trials in randomized order and separated by at least 1 wk. A protocol schematic is illustrated in Fig. 1. Upon arrival to the laboratory, each study volunteer swallowed the telemetry pill and was instrumented for heart rate and skin temperature measurements. Next, the individual was dressed in a tube-lined perfusion suit that permitted the control of body temperature by changing the temperature of water circulating through the suit (Med-Eng, Ottawa, Canada). The perfusion suit covered the entire body with the exception of the head, hands, and feet. On average, suit perfusion began 15 min after ingestion of the telemetry pill. During the HS condition, 46°C water was perfused through the suit until internal temperature increased ~0.6°C (range: 0.5–0.8°C) over 45–60 min. Measures of central conduction and cortical excitability were performed while maintaining internal temperature constant. Following the HS trial, body temperature was normalized to baseline by perfusing cool water through the tube-lined suit. During the TN condition, 34°C water was perfused for a standard time period of 60 min to approximate the time required to increase

\[ J\ Appl\ Physiol \ doi:10.1152/japplphysiol.01119.2012 \ www.jappl.org \]
core temperature during the HS trial. Following the standard time period, measures of central conduction and cortical excitability were performed while core temperature was maintained at resting levels.

Heart rate, core temperature, skin temperatures (chest, back, thigh, and calf), and blood pressure were continuously monitored during each trial. A nine-point thermal sensation (0 = very cold to 8 = very hot) and a five-point thermal discomfort (1 = comfortable to 5 = intolerable) were used to determine the thermal comfort at 10-min intervals throughout each trial (6). In addition, subjective ratings of fatigue were recorded using a 0–100 visual analog scale. MS patients were also monitored, after the HS trial, until body temperature returned to baseline levels and any signs and symptoms had resolved.

**Data Analysis**

Group differences in physical characteristics and underlying fatigue levels were identified using unpaired t-tests. Thermal, cardiovascular, and subjective responses as well as baseline electrophysiological responses were examined with 2 (group) × 2 (treatment) repeated-measures (RM) ANOVA.

Pre- and postfatigue task MEP parameters (MEP$_{lat}$ and CMCT) were initially analyzed using 2 (group) × 2 (treatment) × 2 (time) RM ANOVA. Examination of within-group treatment and time effects was assessed with separate 2 × 2 RM ANOVAs for controls and MS patients. Treatment and group differences in peak force and the T$_{50%}$ were assessed using 2 RM ANOVAs for controls and MS patients. Treatment differences in peak force [(F(1,17) = 11.73, P = 0.003), which

**RESULTS**

**Subject Characteristics**

Although each MS patient was matched to a healthy control for age (within 5 yr), BMI (within 3 units), and physical activity (frequency within 1 day/wk; duration within 30 min/session), the MS group on average had higher BMI and participated in significantly less physical activity than controls (Table 1). Additionally, underlying fatigue levels were significantly higher in MS patients compared with controls (Table 1). In general, MS patients represented an active and mild to moderately impaired subgroup of MS patients.

**Thermal, Cardiovascular, and Subjective Responses**

The HS condition produced significant mean increases in core temperature (0.6°C) and in skin temperature (3.3 and 3.7°C for healthy controls and MS patients) (P < 0.001, Table 2). These responses were paralleled by significant HS treatment effects for thermal sensation (hotter) and thermal comfort (more uncomfortable) in both groups (P < 0.001). Self-reported fatigue increased during HS in both healthy controls and MS patients (P < 0.001), although MS patients reported significantly greater increases in fatigue (0.015). For both groups, heart rate was significantly higher and mean arterial pressure (MAP) was significantly lower during HS (P < 0.001). MAP was significantly higher in MS patients than controls during both treatments (P < 0.05).

**Force**

A significant overall treatment by group interaction was observed for peak force [F(1,17) = 11.73, P = 0.003], which

Table 2. **Thermal, cardiovascular, and subjective responses during HS and TN conditions**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MS</th>
<th>RM ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS</td>
<td>TN</td>
<td>Group P value</td>
</tr>
<tr>
<td>T$_{core}$ °C</td>
<td>37.6 ± 0.25±</td>
<td>37.0 ± 0.37</td>
<td>0.850</td>
</tr>
<tr>
<td>Mean T$_{skm}$ °C</td>
<td>37.0 ± 0.46±</td>
<td>33.8 ± 0.91</td>
<td>0.767</td>
</tr>
<tr>
<td>Thermal sensation</td>
<td>6.9 ± 0.85†</td>
<td>3.7 ± 0.80*</td>
<td>0.025</td>
</tr>
<tr>
<td>Thermal comfort</td>
<td>3.2 ± 1.01†</td>
<td>1.1 ± 0.31</td>
<td>0.107</td>
</tr>
<tr>
<td>Fatigue (0–100)</td>
<td>21 ± 19.5†</td>
<td>10 ± 11.0</td>
<td>0.029</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>85 ± 12.6†</td>
<td>65 ± 8.3</td>
<td>0.238</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>79 ± 6.0*†</td>
<td>82 ± 9.7*</td>
<td>0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HS</th>
<th>TN</th>
<th>Group P value</th>
<th>Treatment P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. RM, repeated measures; HS, heat stress; TN, thermoneutral; T$_{core}$, core temperature; mean T$_{skm}$, mean skin temperature; MAP, mean arterial pressure. *Significant difference from MS for corresponding condition, P < 0.05. †Significant within-group difference from TN condition, determined by post hoc analysis.

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was due to divergent peak force results during HS, with controls showing a small increase [12%, $F(1,8) = 3.44$, $P = 0.101$] and MS patients demonstrating a significant decrease of 22% [$F(1,9) = 8.90$, $P = 0.015$] (see Fig. 2). For $T_{50\%}$, a significant overall treatment effect was observed [$F(1,17) = 5.15$, $P = 0.037$]. Post hoc analyses indicated that $T_{50\%}$ was not affected by the thermal condition in controls [$F(1,8) = 0.52$, $P = 0.523$], but, in MS patients, HS significantly reduced $T_{50\%}$ compared with TN [$F(1,9) = 5.43$, $P = 0.045$, Fig. 2]. The rate of force decline was the same for HS and TN conditions in MS patients due to treatment differences in peak force.

Electrophysiological Measures

Resting measures. There were no significant overall group differences for any resting electrophysiological measure (Table 3). However, significant overall treatment effects were seen for CMAP latency [$F(1,20) = 15.23$, $P = 0.001$], F-wave latency [$F(1,20) = 10.44$, $P = 0.004$], median nerve conduction velocity [$F(1,20) = 15.02$, $P = 0.001$], and RMT [$F(1,20) = 13.21$, $P = 0.002$]. Post hoc analyses indicated that HS resulted in significantly shorter CMAP latency ($P = 0.005$) and faster median nerve conduction velocity ($P = 0.003$) in controls. The HS condition resulted in decreased F-wave latency and increased RMT in both groups but reached statistical significance only in MS patients ($P = 0.046$ and 0.094 for F-wave latency and 0.013 and 0.068 for RMT in MS patients and controls, respectively). No group or treatment differences were observed for cortical SP duration.

Table 3. Resting electrophysiological responses to HS and TN conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>MS</th>
<th></th>
<th>RM ANOVA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS</td>
<td>TN</td>
<td>HS</td>
<td>TN</td>
<td>Group $P$ value</td>
<td>Treatment $P$ value</td>
</tr>
<tr>
<td>CMAP amplitude, mV</td>
<td>13.1 ± 3.7</td>
<td>14.7 ± 4.2</td>
<td>12.4 ± 3.2</td>
<td>11.8 ± 3.5</td>
<td>0.241</td>
<td>0.492</td>
</tr>
<tr>
<td>CMAP latency, ms</td>
<td>3.22 ± 0.49*</td>
<td>3.81 ± 0.61</td>
<td>3.23 ± 0.75</td>
<td>3.61 ± 0.51</td>
<td>0.589</td>
<td>0.004</td>
</tr>
<tr>
<td>Min F latency, ms</td>
<td>26.38 ± 1.56</td>
<td>26.96 ± 1.61</td>
<td>25.63 ± 1.74*</td>
<td>27.08 ± 1.57</td>
<td>0.711</td>
<td>0.008</td>
</tr>
<tr>
<td>Median NCV, m/s</td>
<td>61.4 ± 6.3*</td>
<td>57.6 ± 4.8</td>
<td>58.5 ± 6.4</td>
<td>57.1 ± 5.9</td>
<td>0.495</td>
<td>0.001</td>
</tr>
<tr>
<td>SP Duration, ms</td>
<td>182 ± 13.8</td>
<td>182 ± 11.6</td>
<td>188 ± 12.9</td>
<td>189 ± 17.6</td>
<td>0.262</td>
<td>0.907</td>
</tr>
<tr>
<td>RMT, %</td>
<td>61.0 ± 6.0</td>
<td>60.2 ± 6.6</td>
<td>63.1 ± 8.0*</td>
<td>61.5 ± 7.7</td>
<td>0.583</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means ± SD. Overall RM ANOVA results illustrate Group effects (across HS and TN conditions) and Treatment effects (across groups). Post hoc within-group differences between conditions are indicated. CMAP, compound muscle action potential; Min F, minimum F-wave latency of 20 trials; NCV, nerve conduction velocity; SP, cortical silent period; RMT, resting motor threshold. *Significant within-group difference from TN condition, determined by post hoc analysis.

Pre-post motor fatigue task measures. The overall RM ANOVA indicated no significant group differences for MEMP$_{\text{lat}}$ [$F(1,20) = 0.88$, $P = 0.357$] or CMCT [$F(1,20) = 0.06$, $P = 0.812$]. Separate analyses to examine treatment and time effects were performed for MS patients and controls. Significant within-group treatment effects for MEMP$_{\text{lat}}$ were seen in MS patients [$F(1,10) = 9.33$, $P = 0.012$] and controls [$F(1,10) = 12.99$, $P = 0.005$], with shorter latencies recorded during HS. For CMCT the treatment effect, decreased latency during HS, was significant in controls [$F(1,10) = 11.46$, $P = 0.007$] but not MS patients [$F(1,10) = 0.74$, $P = 0.410$, Table 4]. There were no significant time (pre- to postmotor fatigue task) effects for MEMP$_{\text{lat}}$ or CMCT in controls [$F(1,10) < 0.06$, $P > 0.807$, Table 4]. For MS patients, CMCT and MEMP$_{\text{lat}}$ increased after the fatigue task; however, neither reached statistical significance [$F(1,10) = 3.66$, $P = 0.085$ and $F(1,10) = 4.88$, $P = 0.052$ for CMCT and MEMP$_{\text{lat}}$, respectively].

Recruitment curve. Representative MEP and CMAP traces are shown for a typical control and MS patient during HS and TN conditions, illustrating stimulation intensity and treatment effects (Fig. 3). The overall 4 (intensity) by 2 (treatment) by 2 (group) RM ANOVA revealed significant intensity [$F(3,12) = 34.8$, $P = 0.001$] and intensity by treatment [$F(3,15) = 2.94$, $P = 0.041$] effects, indicating increased MEMP$_{\text{amp}}$ (expressed relative to CMAP amplitude obtained during the same thermal condition) at stimulus intensities above RMT during both TN and HS conditions, with larger increases seen during the TN condition (Fig. 4). Separate RM analyses for MS patients and controls showed significant intensity effects in both groups [$F(1,6, 16) > 25.5$, $P < 0.001$]. Significant treatment and intensity by treatment effects were observed only in MS patients [$F(1,10) = 4.95$, $P = 0.050$ and $F(2,9, 28.5) = 4.24$, $P = 0.015$, respectively]. Post hoc contrasts included in the RM model indicated that in MS patients during HS, MEMP$_{\text{amp}}$ were significantly lower at 120 and 130% of RMT [$F(1,10) > 6.18$, $P < 0.032$]. In controls, treatment and intensity by treatment effects were not statistically significant [$F(1,10) < 1.10$, $P > 0.360$; Fig. 4].

Recruitment curve slope was determined from the steepness of the regression line through individual response curves during HS and TN conditions. RM ANOVA of recruitment curve slope indicated a significant treatment effect [$F(1,20) = 4.52$, $P = 0.046$] but no group differences or treatment by group interaction [$F(1,20) < 1.48$, $P > 0.239$]. In MS patients, recruitment curve slope was significantly reduced during HS compared with TN [$T_{50\%} = 3.13$, $P = 0.011$; Fig. 4, inset].

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**PED.** In MS patients, the HS condition resulted in significantly lower baseline MEP_{amp} (expressed relative to CMAP amplitude) compared with the TN condition \((P < 0.05)\) and compared with controls during both treatments \((P < 0.05; \text{Fig. } 5, \text{ left})\). HS had no significant effect on baseline MEP_{amp} in healthy controls.

Recovery MEP_{amp} were recorded at 1, 4, 6, 8, and 10 min after the fatigue task and are expressed relative to preexercise levels (Fig. 5, right). In controls, RM ANOVA indicated a significant time effect \([F(3.1, 30.6) = 6.14, P = 0.002]\) but no treatment effect \((P > 0.05)\) and treatment by time interaction \([F(3.3, 32.1) = 0.38, P = 0.781]\); for postexercise MEP_{amp}. Contrasts included in the ANOVA model showed that MEP_{amp} were significantly lower relative to baseline at all recovery time points in controls \((P < 0.002)\) for the MS group, significant time \([F(5.50) = 16.13, P < 0.001]\), treatment \([F(1.50) = 4.95, P = 0.050]\), and treatment by time interaction \([F(2.7, 27.2) = 3.84, P = 0.024]\) effects were observed. Contrasts derived from the treatment by time interaction illustrate significantly different treatment responses in MS patients at 1, 4, 6, and 10 min postexercise \([F(1.10) > 4.99, P < 0.049]\), with smaller relative decreases in postexercise MEP_{amp} during HS compared with TN (Fig. 5, right).

These smaller relative postexercise decreases in the MS group during HS reflect baseline differences in MEP_{amp} (Fig. 5, left).

**DISCUSSION**

To our knowledge, this is the first study to directly assess the effect of passive heat exposure on central conduction and cortical excitability in MS patients. The passive HS employed in the study produced significant perceptual changes, including increased subjective fatigue in both MS patients and healthy controls. Fatigue ratings during HS were significantly higher in MS patients than controls. It is important to note that fatigue perception increased significantly at rest, well before the motor fatigue task, suggesting that the effects of thermal stress were responsible. This is consistent with reports of heat-sensitive MS patients who experience greater fatigue when exposed to warm environments.

In addition to increased fatigue perception, reductions in peak force and faster decline in force were observed in MS patients during HS and are likely due to CNS lesions that are affected by heat, which could lead to recruitment of fewer motor units (conduction block) (11). In controls, there were no heat-related differences in peak force or force decline, which is in contrast to Nybo and Nielsen’s work showing that, in healthy individuals, sustained maximal voluntary force declined significantly faster during hyperthermia (19). There are several possible explanations for this discrepancy. One possibility is that the degree of HS in the present study was not sufficient to appreciably decrease central drive in healthy individuals. In the study by Nybo and Nielsen, the degree of hyperthermia was substantially higher, core temperature of 40°C, compared with the moderate level in the present study.

In addition, hyperthermia was achieved actively, altering peripheral metabolic characteristics that could further influence peak force. Still, other studies (16, 33) have demonstrated progressive decreases in MVC and voluntary activation with increasing core temperatures in the range of the present study. It is possible that mechanisms of task failure for the small hand muscles used in the present study differ from those of the knee extensors and plantar flexors of those studies (7, 16).

In healthy controls, resting MEP_{lat} and CMCT were significantly shorter during the HS condition, reflecting increased peripheral and central nerve conduction velocity that is consistent with previous work that showed linear increases in conduction velocity of healthy nerve fibers with increasing temperature in the range of 28–40°C (22). In contrast, HS
resulted in increased peripheral conduction velocity in MS patients, but no change in CMCT. In demyelinated neurons, studies have shown that increased temperature reduces the conduction safety factor and can produce conduction slowing and/or conduction block (11, 22, 29). For MS patients, the apparent inability of central pathways to increase conduction velocity during conditions of increased core temperature may reflect altered conduction characteristics due to demyelination in the CNS. Interestingly, the additional demands of sustained motor activity appear to amplify these effects in MS patients, as evidenced by trends toward increased MEP_{lat} (P = 0.052) and CMCT (P = 0.085) immediately following the motor fatigue task. Similarly, our previous work showed temporary functional declines in motor performance following combined arm/leg cycling exercise even when core temperature increases were prevented (36). This suggests that both sustained and
intermittent motor activity can alter central conduction characteristics and ultimately impair task performance in MS patients.

Recruitment curve characteristics paralleled fatigue perception and decreases in force production in that cortical excitability, indicated by recruitment curve slope, decreased in MS patients during HS. Proposed mechanisms to explain the effect of HS on cortical excitability include alterations in output from thermoregulatory centers in the hypothalamus or other structures, including the motor cortex (19, 23, 34). In the context of the present study, these explanations are somewhat problematic because the HS condition did not reduce cortical excitability in healthy controls (Fig. 4). The small range of stimulus intensities used to determine recruitment curves used in the present study as described by Chen et al. (3) may have resulted in an overall underestimation of slope due to missing responses evoked at higher stimulation intensities. Although this explanation could account for the lack of a thermal effect in controls, it is also possible that the degree of HS was not sufficient to produce central fatigue in controls. This is consistent with the controls’ force characteristics, which also suggest that the degree of HS in the present study did not increase fatigue. Nonetheless, a more extensive recruitment curve that included higher stimulus intensities would have clarified this issue.

The significant reduction in recruitment curve slope in MS patients during HS was expected and corresponds to reports of increased symptomatology with increased temperature (11). It is reasonable to assume that demyelinated pathways in the CNS respond to increased temperature similarly to demyelinated peripheral nerve, with small increases in temperature capable of blocking of action potentials (11). The observed increase in RMT in MS patients during HS supports this concept.

Changes in cortical SP duration reflect spinal and cortical inhibitory mechanisms (9). Taylor et al. observed SP prolongation during sustained MVC of elbow flexors attributed to net decreases in cortical output, most likely due to intracortical inhibition (ICI) (31, 32). In the present study, SP duration was not affected by HS in either group. Using paired pulse TMS, Liepert and colleagues observed decreased postexercise ICI in MS patients with fatigue but no changes in cortical SP and suggested that SP duration was dependent on inhibitory mechanisms independent from those involved with ICI (14). HS and/or fatiguing exercise may influence different inhibitory circuits than those assessed using cortical SP.

Both MS patients and healthy controls demonstrated PED of evoked potentials. This has been documented in previous studies and is thought to indicate decreased cortospinal excitability (13, 14, 21). The intracortical mechanism for PED may be analogous to the spinal mechanisms of postactivation depression of the H-reflex, including possible depletion of the available neurotransmitter pool or increased presynaptic inhibition (27). Postexercise changes in cortical excitability may also be influenced by peripheral signaling from group III/IV afferents that inhibit motor areas (18). Temperature-sensitive TRP receptors are present on these afferent fibers and interact with metabolite-detecting ASIC and P2X receptors and thus could enhance inhibitory afferent signaling (15).

No treatment effects were evident for postexercise MEP responses in healthy controls, but in MS patients HS produced blunted MEP amplitudes at baseline and at all postfatigue task time points. As mentioned earlier, HS in combination with sustained contractions results in even greater decrements in central activation (4, 17, 19). It would be useful to examine measures of cortical excitability at a range of temperatures produced both passively and during active conditions to examine the additional effect of peripheral signaling from muscle afferents on central responses.

To summarize, mild passive HS resulted in greater fatigue perception and impairments in force production in MS patients and corresponding evidence for cortical degeneration or dysfunction, including significantly increased RMT, decreased MEPamp, and decreased recruitment curve slope (35). PED of MEPamp was evident in controls and MS patients; however, the combination of HS and sustained exercise magnified these decrements in MS patients. Taken together, these results suggest that CNS pathology in MS patients played a substantial role in reducing cortical excitability. Central conduction (CMCT) was significantly shorter during HS in healthy controls; however, in MS patients, normal increases in conduction velocity with increased temperature were not observed centrally. Both groups exhibited increased peripheral nerve conduction velocity, supporting the concept that differences between MS patients and controls were of central origin.

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DISCLOSURES
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AUTHOR CONTRIBUTIONS

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