



RESEARCH PAPER



## Performance in complex motor tasks deteriorates in hyperthermic humans

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### ABSTRACT

Heat stress, leading to elevations in whole-body temperature, has a marked impact on both physical performance and cognition in ecological settings. Lab experiments confirm this for physically demanding activities, whereas observations are inconsistent for tasks involving cognitive processing of information or decision-making prior to responding. We hypothesized that divergences could relate to task complexity and developed a protocol consisting of 1) simple motor task [TARGET\_pinch], 2) complex motor task [Visuo-motor tracking], 3) simple math task [MATH\_type], 4) combined motor-math task [MATH\_pinch]. Furthermore, visuo-motor tracking performance was assessed both in a separate- and a multipart protocol (complex motor tasks alternating with the three other tasks). Following familiarization, each of the 10 male subjects completed separate and multipart protocols in randomized order in the heat (40°C) or control condition (20°C) with testing at baseline (seated rest) and similar seated position, following exercise-induced hyperthermia (core temperature  $\sim 39.5^\circ\text{C}$  in the heat and  $38.2^\circ\text{C}$  in control condition). All task scores were unaffected by control exercise or passive heat exposure, but visuo-motor tracking performance was reduced by  $10.7 \pm 6.5\%$  following exercise-induced hyperthermia when integrated in the multipart protocol and  $4.4 \pm 5.7\%$  when tested separately (both  $P < 0.05$ ). TARGET\_pinch precision declined by  $2.6 \pm 1.3\%$  ( $P < 0.05$ ), while no significant changes were observed for the math tasks. These results indicate that heat per se has little impact on simple motor or cognitive test performance, but complex motor performance is impaired by hyperthermia and especially so when multiple tasks are combined.

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cognitive test; core temperature; cognition; heat stress; heat strain; hyperthermia; motor performance; task complexity; visuo-motor tracking

### Introduction

Heat stress, and the associated body hyperthermia, has marked effects on whole-body exercise performance, with increased cardiovascular strain, impaired ability to maintain maximal motor activation and changes in neuromuscular activation as three of the apparent parameters influencing fatigue provoked by overheating.<sup>1–12</sup> For endurance activities, these findings are consistently reported both for ecological outdoor settings with performance evaluated in real competitions, or assessed via simulated races in the heat.<sup>6,13–15</sup> Parallel performance effects are also reported in mechanistic studies in laboratory settings where the physiological impact of heat in indoor studies is usually higher because low circulating wind speeds in simulated settings exacerbate the heat stress and impact on human

thermoregulation.<sup>1</sup> In contrast, for tasks not involving prolonged or maximal physical exertion, but rather depending on attention or executive functions, there appears to be some discrepancy between the marked reductions in occupational productivity and reported loss of working capacity in ecological settings,<sup>16–23</sup> and the unchanged performances reported for simple choice-reaction tests or semi-complex cognitive testing in the lab.<sup>17,22,24–26</sup>

The discrepancy between occupational observations and controlled testing under stressful environmental conditions could relate to the lack of control for dehydration or other confounding factors, or a lack of sensitivity in the test protocols used. The latter is of particular importance so that the knowledge obtained in laboratory-based observations can be effectively transferred to real-life scenarios.<sup>27</sup> It is possible that

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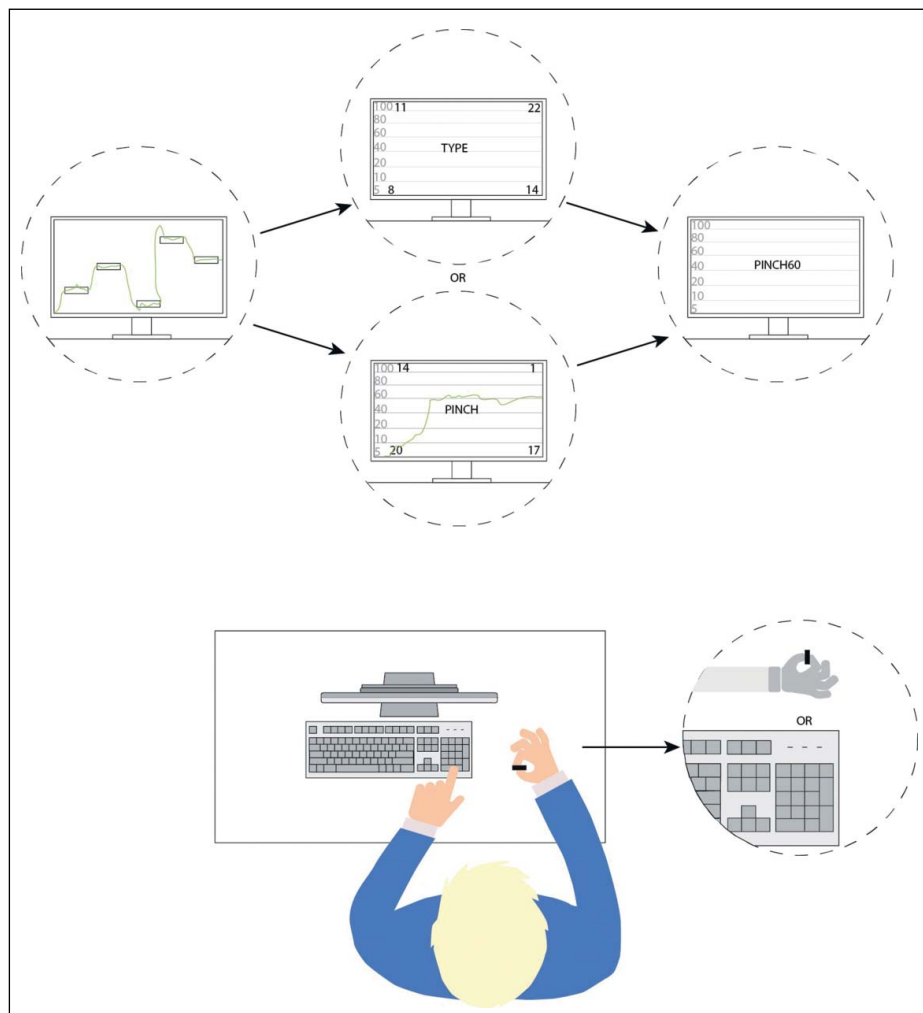
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the discrepancy could to some extent relate to task complexity where lab-based cognitive tests often involve more or less stereotyped tasks, repeated over time, and with outcome measures mainly relying on a simple motor response, whereas occupational settings often alternate and involve more or less complex and demanding motor responses.<sup>27</sup>

Performance measured as reaction time in simple reaction or choice-reaction tests is usually unaffected or slightly faster in the heat, as nerve conduction velocity and neural transmission (all chemical reactions) benefit from higher body temperatures. In contrast, Racinais and coworkers report that hyperthermia impairs short-term memory<sup>28</sup> (i.e. performance in a more complex

cognitive task<sup>17</sup>). Thus, the influence of heat stress on tasks engaging motor performance and cognition seems to be task-dependent and, specifically, depend on the complexity of the task involved.<sup>18,20,21,29</sup> However, no study has characterized the impact of hyperthermia on separate and combined motor and cognitive tasks involving e.g. processing of visual input, problem solving and the ability to complete the tasks with an appropriate motor response, which characterize many occupational tasks and everyday activities.

The aim of this study, therefore, was to develop a test protocol capable of detecting the effects of hyperthermia on motor and cognitive test performance among a range of task complexities. To this aim, we modified a



**Figure 1.** Illustration of the motor-math protocol of the present study. e.g. to the left an illustration of the visuo-motor tracking task (VMT), where the 5 boxes/targets appears on the screen 1 s before the 12 s tracking begins. The cursor (green line) moves from left to right over the screen (fixed velocity) and the subject is instructed to adjust force on the strain gauge transducer to keep the cursor within the designated box. In the “separate protocol”, this task then repeats 40 times with the position of the boxes randomly changed from trial to trial, whereas in the multipart protocol, the VMT alternates with the MATH\_type, MATH\_pinch or TARGET\_pinch tasks. During VMT, MATH\_pinch and TARGET\_pinch, subjects used the strain gauge, whereas in the MATH\_type the number pad was used (bottom pic, right).

visuo-motor tracking (VMT) test setup<sup>30-32</sup> to develop a protocol [multipart protocol] consisting of VMT, combined with math-motor tasks [pinch and type] and an additional TARGET\_pinch task, which in a semi-randomized order appeared on the working computer screen in front of the participants (see Fig. 1). The multipart protocol was designed to mimic occupational settings, where task often alternates during the day. Furthermore, the influence of heat stress and hyperthermia was compared to effects evaluated during a “separate protocol” consisting only of the VMT task (see Fig. 1, pic. 1). This to compare simple testing with complex testing involving alternating tasks.

We hypothesized that hyperthermia would deteriorate performance in complex tasks (represented by Visuo-motor tracking and MATH\_pinch testing), whereas simpler tests such as TARGET\_pinch and MATH\_type would remain unaffected. Furthermore, that VMT performance would be more vulnerable to hyperthermia when completed in a multipart protocol with tests alternating compared to separate VMT testing.

## Materials and methods

### Subjects

Ten healthy untrained males (Age;  $29 \pm 5$  years, body mass;  $83.3 \pm 11.5$  kg) participated in the present study. All subjects were informed of any risks and discomfort associated with the experiment before they provided written consent to participate in this study, approved by the National Committee on Health Research Ethics (*protocol number: 55907\_v3\_02012017*).

### Experimental design

Before commencing the experimental trials, each subject was familiarized to the motor-cognitive test battery (described below) and completed a heating trial in the lab at a room temperature of  $40^\circ\text{C}$  to become familiar with heat exposure and the various procedures. The familiarization protocol consisted of 2 days with 500 pre-trials (in total) of the visuo-motor tracking tasks (with familiarization verified by no change in performance from 400 to 500 trials), to minimize the influence from further learning effects during the experiment. Thomas et al. 2016<sup>30,33</sup> report a significant within-session learning effect in the VMT task from baseline to immediate retention (46%

increase in mean score) and a significant offline increases in mean score in the group exercising with high intensity following motor skill acquisition compared with control. This demonstrates the necessity of the familiarization procedure in the present experiment.

Subjects were unaware of the researcher’s hypotheses and naive to the purpose of the study, but for obvious reasons, the subjects were not blinded to the treatment (heat/control conditions).

Subjects completed a motor and cognitive test battery (different tasks specified below) in four different conditions; 1) CON\_baseline, 2) CON\_norm, 3) HEAT\_baseline, 4) HEAT\_hyper, with all testing conducted in an environmental chamber (University of Copenhagen, DK) (see Table 1). The subjects were randomly allocated to either start in HEAT- ( $\sim 40^\circ\text{C}$ ) or CON ( $\sim 20^\circ\text{C}$ ) and then crossover on the subsequent experimental day.

For each subject, experimental days were separated by at least two days and all testing (familiarization and experimental trials, HEAT and CON) completed within one month. In all conditions the subjects completed baseline motor-cognitive tests (CON/HEAT\_baseline) followed by 1 hour of ergometer cycling (100 W,  $\sim 80$  rpm), to increase core temperature ( $T_{\text{core}}$ ) by  $\geq 1^\circ\text{C}$  in CON (a normal working/exercise temperature response) and  $\sim 2^\circ\text{C}$  in HEAT\_hyper (a hyperthermic condition), before repeating the motor-cognitive tests in a resting/seated position (as illustrated on Fig. 1).

All subjects arrived to the lab  $\sim 30$  min. before the start of the experiment. Subjects then emptied their bladder, completed questionnaires with thermal comfort rating (TC) and temperature sensation rating (TS), were weighed (without clothes), before a resting heart rate measure was obtained prior to entering the

**Table 1.** Rectal temperature ( $T_{\text{core}}$ ) in Celsius  $\pm$  SD. Body weight (BW) in kilograms  $\pm$  SD. Heart rate (HR) in beats per minute  $\pm$  SD. Thermal comfort rating (TC)  $\pm$  SD and Temperature sensation rating (TS)  $\pm$  SD.

	CON		HEAT	
	baseline	norm	baseline	hyper
$T_{\text{core}}$ ( $^\circ\text{C}$ )	$37.4 \pm 0.3$	$38.2 \pm 0.3^*$	$37.4 \pm 0.3$	$39.5 \pm 0.3^*\$$
BW (kg)	$84.7 \pm 11.4$	$84.6 \pm 11.4$	$84.6 \pm 11.7$	$84.7 \pm 11.5$
HR (bpm)	$69 \pm 10$	$94 \pm 29^*$	$81 \pm 11^{\$}$	$140 \pm 25^*\$$
TC	$0 \pm 0$	$0.5 \pm 0.5^*$	$0.5 \pm 0.5^{\$}$	$3.0 \pm 0.5^*\$$
TS	$-0.5 \pm 0.5$	$0.5 \pm 1.0^*$	$1.0 \pm 0.5^{\$}$	$3.0 \pm 0.0^*\$$

\*Denotes significant different from baseline,  $^{\$}$  significant difference between baseline conditions and  $^{\$}$  significant different from CON\_norm, ( $P < 0.05$ ).

climatic chamber. On the experimental days, in both HEAT and CON, the subjects were seated for 15 min in an office chair and completed 40 further familiarization trials before they initiated the baseline testing. Following completion of the baseline testing, the subject transferred to an ergometer bicycle (Monark Ergonomic, E839) and started cycling at a fixed load (100 W corresponding to a metabolic heat production of ~400 W) with a steady cadence ~80 rpm. During both conditions, the subjects ingested water with a temperature of ~37°C to prevent dehydration without directly influencing the core temperature response. Following 1 h of exercise, the subject returned to the office chair and remained seated for 5 min before commencing the motor-cognitive test battery. Post exercise, the subjects wore rain clothing to ensure that the core temperature remained stable during the post-tests in both trials (at respectively ~38.2 and 39.5°C)

### **Motor performance and cognitive testing (multipart protocol)**

The multipart protocol consisted of four different task i.e. visuo-motor tracking (VMT), MATH\_type, MATH\_pinch and TARGET\_pinch. The protocol always started with a VMT task, thereafter a MATH\_type or MATH\_pinch and every sequence finish with a TARGET\_pinch task (Fig. 1) and continued for 120 “sequences” i.e. 40 series of 3 task sequences (separated by 3 s break between each sequence). The separate protocol consisted of only the VMT task (40 sequences repeated with 3 s break between each tracking).

During all motor-cognitive tests, subjects were seated on an office chair, looking at a 24-inch Samsung computer monitor. The subject used the preferred (dominant) hand both for the pinching and typing tests. In the present study, all subjects were right-handed, however the setup allow for testing of left-handed subjects as the moveable pinch grip permit for changing position. Force was applied to a strain gauge (Dacell, model UU3-K5, 5 Kgf), connected to a strain amplifier (Dacell, DN-AM-310) and the signal was subsequently digitized and sampled at 500 Hz, with a data acquisition board, NI-USB-6008 (National instruments inc., USA). A customized script built on PYTHON (Python software foundation, USA) was used for running the protocol.

The VMT (visuo-motor-tracking test) task consisted of five boxes (see Fig. 1), indicating the targets that subjects were instructed to adjust the pinching force to match as accurately as possible and keep the cursor within the specified box and adjust force as fast as possible when the cursor moved to the next box and so forth. For the VMT, the primary outcome variable is the percentage of total time on target (percent of the 12 seconds the subject provided correct force), the total time on target i.e. within the five boxes was calculated and the score expressed in percentage “*time on target*”, (i.e. 100 percent equaled full time inside all five targets).

In the MATH\_pinch (combination of – MATH\_type and TARGET\_pinch) and MATH\_type tasks (see Fig. 1) four numbers (ranging from 1–25), were displayed in each corner of the computer monitor. The subjects were then required to type the result in the MATH\_type task and pinch (adjust force via the strain gauge transducer) in the MATH\_pinch task – and keep the cursor at the result-target force for 6 s (score was average over the last 6 s).

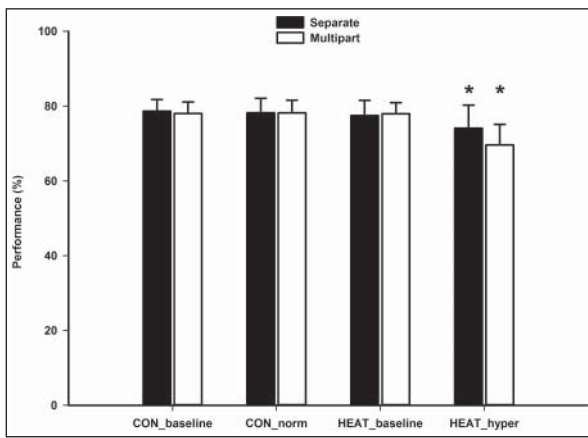
Similarly, a TARGET\_pinch task (Pinch[number]) was performed where the number refers to the target force that the subject was required to adjust the force level to. The number changed from one sequence to the next and was displayed on the screen for 6 s and the subject then adjusted and maintained that force for a further 6 s.

For the MATH\_type, MATH\_pinch and TARGET\_pinch test the score is the percentage of the correct answer, i.e. for these tests 100% is the best possible score (if the exact sum is typed or provided via the pinch force).

Each task lasted for 12 s (VMT, MATH\_type, MATH\_pinch and TARGET\_pinch) and, following each task, visual feedback (1 s) of the performance was provided with the score appearing in the bottom right corner of the screen and 2 s of transition time to next task, e.g. 10 min. of testing in the separate protocol and 30 min. of test duration in the multipart protocol, this to ensure 40 trials of each task.

The lower baseline scores for the complex tasks (VMT and MATH\_pinch) compared to the simple tests (MATH\_type and TARGET-pinch) signified that the complex tests were more challenging and difficult to execute than the simple tests (see Figs. 2 and 3).

$T_{core}$  was continuously measured with a rectal thermometer (Ellab Copenhagen, CTD85) inserted 7–10 cm beyond the anal sphincter.



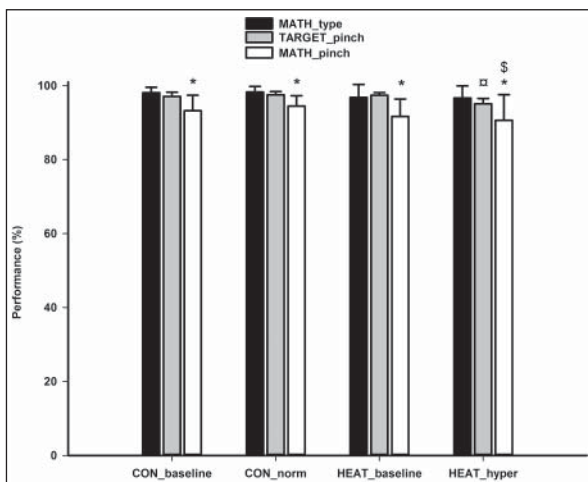
**Figure 2.** VTM during thermoneutral (CON\_baseline and CON\_norm) and heat (HEAT\_baseline and HEAT\_hyper) for both separate and multipart protocol. Values are means plus SD for each condition. \* Significant different from baseline and CON\_norm conditions.

### Hydration

Changes in body mass were used as an index of hydration and to avoid (minimize) any dehydration and/or interference with the core temperature, the subjects were required to drink water equal to expected sweat loss (estimated from their familiarization trials). Body mass was assessed using a platform scale (InBody 270, InBody CO Ltd).

### Thermal comfort and sensation

All subjects filled out questionnaires before and after the cognitive test-battery. The questionnaires were



**Figure 3.** MATH\_type, TARGET\_pinch and MATH\_pinch during thermoneutral (CON\_baseline and CON\_norm) and heat (HEAT\_baseline and HEAT\_hyper). Values are means plus SD for each condition. \* Significant lower task score within condition, \$ significant different from CON\_norm, □ significant different from all baseline and CON\_norm.

standardized (ASHRAE standard 55), for thermal comfort rating (TC) and temperature sensation rating (TS).

### Statistical analysis

Changes across conditions for the test scores i.e. VMT, MATH\_pinch, MATH\_type and TARGET\_pinch were evaluated by two-way analysis of variance test with conditions (CON/HEAT) and time (baseline-norm/hyper) interaction as fixed effects and subject-specific as random effects were fitted. When a significant main effect in the ANOVA was found, post-hoc pairwise comparisons for each block were performed with the Bonferroni correction test. Paired T-test for comparison of  $T_{core}$ , BW, HR, TC and TS for baseline/post and separate/multipart, respectively. All statistical analyses were carried out in Sigmaplot (© 2014 Systat Software Inc.).

### Results

The four different test conditions were established and characterized by stable and similar core temperature during CON\_baseline and HEAT\_baseline ( $37.4 \pm 0.3^\circ\text{C}$  and  $37.4 \pm 0.3^\circ\text{C}$ , respectively), and increased for CON\_norm (to  $38.2 \pm 0.3^\circ\text{C}$ ) and further elevated (to  $39.5 \pm 0.3^\circ\text{C}$ ) in the HEAT\_hyper condition (see Table 1 for overview).

Thermal comfort rating (TC) was similar during baseline conditions, but followed the same pattern as the core temperature increasing over time ( $P < 0.05$ ) and across conditions (see Table 1 for overview).

Temperature sensation rating (TS) was already different at baseline, with higher rating in the heat compared to control ( $P < 0.05$ ). Furthermore TS increase during both CON\_norm and HEAT\_hyper but with TS remaining higher in the heat compared to control ( $P < 0.05$ ) and attaining an average score of 3 in the HEAT\_hyper condition corresponding to “HOT” and the maximal scoring on the scale.

### Heart rate (HR)

The heart rate was higher in the HEAT\_baseline compared to CON\_baseline ( $P < 0.01$ ). HR was elevated ( $P < 0.001$ ) during CON\_norm and HEAT\_hyper, compared to baseline conditions. HR during HEAT\_hyper was even higher ( $P < 0.001$ ) compared with CON\_norm.

### Performance in motor and cognitive tasks

VMT performance was impaired in the HEAT\_hyper condition with a  $10.7 \pm 6.5\%$  reduction in the multipart protocol ( $P < 0.001$  compared to both baselines and the time matched CON\_norm condition) and  $4.4 \pm 5.7\%$  in the separate protocol ( $P < 0.05$  vs. baseline and  $P < 0.01$  vs. CON\_norm; see Fig. 2.)

TARGET\_pinch was lower in HEAT\_hyper compared to the other three test conditions ( $P < 0.001$ ; see Fig. 3), whereas neither exercise (CON\_baseline vs CON\_norm) nor environmental temperature per se (CON vs HEAT\_baseline) influenced TARGET\_pinch performance. MATH\_pinch performance tended to follow the same pattern of response as the TARGET\_pinch, with observed difference between HEAT\_hyper and CON\_norm ( $P < 0.05$ ), but the variation for this test was higher and no other differences was observed ( $P > 0.1$ ) for either the MATH (pinch or type) across trials.

For the MATH\_type task the subjects tended to provide the results slightly (770 ms) faster in the HEAT\_hyper compared to CON\_baseline ( $P = 0.051$ ), but no other tendencies or significant differences were observed between conditions for the math tasks.

Evaluated across all conditions, the average baseline scores in the VMT and MATH\_pinch task was  $78.0 \pm 3.2\%$  and  $92.9 \pm 4.9\%$ , respectively, and hence lower ( $P < 0.01$ ) than the average scores in the MATH\_type ( $97.7 \pm 2.6\%$ ) and TARGET\_pinch ( $96.8 \pm 1.4\%$ ).

### Discussion

The present study demonstrates that hyperthermia impairs performance in complex motor tasks and the impact seems to increase when the visuo-motor tracking task alternates with other assignments in the test protocol. Passive heat exposure, with slightly elevated thermal sensation and no change in core temperature i.e. HEAT\_baseline, did not impair VMT performance, nor was motor performance impaired following exercise in control conditions, despite a moderate elevation in thermal discomfort and a  $\sim 1^\circ\text{C}$  increase in  $T_{\text{core}}$ .

In contrast, impaired ability to adjust force to a visual input became evident when the combined environmental and metabolic heat stress resulted in profound hyperthermia. For the simple target task (TARGET\_pinch) the influence was minor, but the influence of hyperthermia appeared to increase with

increasing task complexity. Thus, the larger impairment of VMT performance in the HEAT\_hyper condition and aggravated effect in the protocol with alternating tasks supported our hypothesis that complex task conditions would be more vulnerable to hyperthermia than simple task conditions. However, in contrast to our hypothesis this did not directly disturb MATH\_pinch performance, but emerged as increased difficulty to maintain performance in the VMT task.

Prolonged test duration or general tasks interference in the protocol with alternating tasks, could potentially influence the present observations. However, during the familiarization trials and in pilot studies, we observed that VMT performance could be maintain for 100 or even 200 consecutive trials (i.e.  $\sim 1$  hour of repeated visuo-motor tracking similar to the separate protocol) when subjects were tested in resting conditions in the heat. Furthermore, the average VMT scores were similar in the multipart and separate protocol in the test conditions where hyperthermia was absent (CON and HEAT baseline) or when the change in core temperature was moderate (see Fig. 2). Therefore, it appears that the pronounced influence of heat stress on VMT performance in the multipart protocol relates to the combination of complex/alternating tasks and the magnitude of hyperthermia. This provides new insight to the interference between tasks and impact of heat stress and it may explain some of the differences and discrepancies between previous observation from stereotypical lab testing and ecological/occupational settings where tasks often alternates.

In addition, only male subjects were included in the present study to minimize influence from hormonal variation and associated changes in baseline core temperature. We expect that women will respond similar to men, but the impact of a given heat stress may vary across different phases of the menstrual cycle.

We chose the VMT test as a complex motor task<sup>17</sup> that would involve activation of several brain areas and rely on the interaction between visual, motor and sensory cortices via subcortical networks<sup>34</sup> as indicated by TMS, fMRI and EEG studies.<sup>31,35-39</sup> Math solving tasks are associated with activation of additional brain areas,<sup>17</sup> and we hypothesized that this could directly influence test performance in the MATH\_pinch test, as this test would rely on the ability to combine cognitive processing of a visual input

with an appropriate motor output. The overall score in the MATH\_pinch test was on average lower than those in the separate tasks (MATH\_type and TARGET\_force; see Fig. 3). This indicates that the combined task was more difficult than the simple tests but, in contrast to the VMT, performance in the MATH\_pinch test was not directly influenced by hyperthermia despite being integrated in the same complex protocol. Further studies are needed to delineate these contrasting findings, but it indicates to us that it is not a simple function of involved brain regions. Functional brain imaging indicate that when so-called cognitive tasks are performed with superimposed heat stress they induce or require higher activation of some brain areas, reflecting increased activity to maintain the same performance.<sup>40</sup> Conversely, hyperthermia lowers cerebral blood flow<sup>3,41,42</sup> and involvement of more brain areas could challenge the ability to increase regional blood flow in activated areas. However, Schlader et al<sup>43</sup> reported that although baseline CBF was lower, hyperthermia did not attenuate the increase in cerebral perfusion during simple cognitive activation. It should though be noted that performance was not impaired in that study, and it is possible that the present protocol with more complex task conditions (alternation between tasks) may introduce “competition” between the activated areas for the available blood flow.

Faster nerve conductance respectively reductions in half relaxation time are other factors that may influence the ability to provide appropriate motor activation in the current motor tasks and influence the ability to maintain maximal motor activation during sustained contractions.<sup>3,28,44,45</sup> While it may become more difficult to sustain maximal activation during a MVC (higher firing frequencies required) the faster nerve conductance may benefit reaction time during so-called simple cognitive tasks.<sup>17,22,25,26</sup> In accordance, we observed a tendency towards decreased reaction time, during MATH\_type task, however this did not benefit the ability to rapidly and accurately adjust force to a visual input. The reduced motor performance in the present study could arise from changes within the neural circuit, which is evident in earlier studies e.g. adjustment in force frequency, reduction of the H-reflex and lowering of EMG signal during maximal voluntary contraction associated with reduction in voluntary activation percentage after

hyperthermia compared to control.<sup>3,9-11</sup> We consider that these changes within the neural circuit may be involved in the impaired motor performance i.e. when an appropriate motor skill pattern is acquired (after intensive familiarization), as small changes within the circuit of this pattern would alter the outcome.

The purpose of the present study was to develop a protocol that had the possibility to: 1) testing of different executive functions and identifying their combined and separate sensitivity to hyperthermia, 2) Allow for studying how simple versus combined/complex motor tasks are affected in the heat. Although further studies are warranted for identifying the underlying mechanisms, the present findings may already have direct practical implications. On the basis of the present observations, we propose that at work places where it is possible to reschedule occupational tasks or for individual planning of a working day, it is worth to consider if tasks complexity can be reduced during periods with high heat stress. Specifically, complex tasks may be scheduled to the time of the day when the environmental heat stress is at a nadir, whereas simpler tasks may be performed during periods with elevated heat load with no or only minor influence on productivity or precision/quality of the work. This may not be an option in all occupational settings where heat stress is an issue, but given the negative impact of environmental heat stress on productivity in many industries,<sup>46,47</sup> it is advisable to develop coping strategies that allows minimizing the influence on productivity and safety.

Based on the results from the present study, we conclude that simple motor task performance as well as performance in more complex motor tasks may be maintained during passive moderate heat exposure and following moderate elevations in the internal temperature. However, when heat stress result in profound hyperthermia the ability to perform tasks relying on motor accuracy becomes impaired and the effects appears to aggravate if complexity of the motor task increases and further decrements are observed with increasing task conditioning complexity.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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