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Hyperthermia does not alter the increase in cerebral perfusion during cognitive activation

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Abstract

This study tested the hypothesis that hyperthermia attenuates the increase in cerebral perfusion during cognitive activation. Mean middle cerebral artery blood velocity (MCA V_{mean}) served as an index of cerebral perfusion, while the nBack test (a test of working memory) was the cognitive task. Hyperthermia was characterized by elevations ($P < 0.001$) in skin (by $5.0 \pm 0.8^\circ\text{C}$) and intestinal temperatures (by $1.3 \pm 0.1^\circ\text{C}$) and reductions ($P < 0.020$) in mean arterial pressure (by 11 ± 10 mmHg), end-tidal CO_2 tension (by 3 ± 6 mmHg) and MCA V_{mean} (by 10 ± 9 cm s^{-1}). Hyperthermia had no influence on nBack test performance (mean difference from normothermia to hyperthermia, $-1 \pm 11\%$; $P = 0.276$) or, counter to the hypothesis, the increase in MCA V_{mean} during nBack testing (mean difference from normothermia to hyperthermia: 0 ± 16 cm s^{-1} ; $P = 0.608$). These findings indicate that the capacity to increase cerebral perfusion during cognitive activation is unaffected by hyperthermia.

Introduction

Upon the initiation of a cognitive task, a cascade of cerebral events unfolds. This cascade commences with increases in neural and metabolic activity that are ultimately accommodated by increases in cerebral blood flow (Girouard & Iadecola, 2006; Rosengarten *et al.* 2012). This ‘coupling’ between cognitive activation and cerebral perfusion enables the cognitive task to be suitably accomplished. Interestingly, however, the capacity to increase cerebral perfusion during cognitive activation is modulated by changes in baseline (i.e. before cognitive activation) blood flow. For instance, chronic suppression of resting cerebral perfusion (by 10–20%) is accompanied by an impaired increase in cerebral perfusion during cognitive activation in healthy older individuals (Sorond *et al.* 2008) and in patients with essential hypotension (Duschek & Schandy, 2004). Acute reductions in brain blood flow,

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Competing interests

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induced via hypocapnia, likewise attenuate the increase in perfusion during a subsequent cognitive task (Szabo *et al.* 2011). On the contrary, however, acute elevations in resting perfusion, whether induced via hypercapnia (Rosengarten *et al.* 2003), acetazolamide (Yonai *et al.* 2010) or exercise (Willie *et al.* 2011*b*), have little impact on the increase in cerebral perfusion in response to such tasks. Thus, it is clear that acute or chronic reductions in cerebral perfusion deleteriously affect the capacity to increase perfusion during cognitive activation.

Hyperthermia, i.e. elevations in both mean skin and internal temperatures, reduces resting cerebral perfusion by 10–30% (Wilson *et al.* 2006; Brothers *et al.* 2009; Nelson *et al.* 2011). This decrease is, at least partly, a result of hypocapnia occurring concomitant to hyperthermia-induced hyperventilation (Fujii *et al.* 2008; Brothers *et al.* 2009; Ross *et al.* 2012). Given that hyperthermia is characterized by reductions in cerebral perfusion and hypocapnia, and that hypocapnia, alone, attenuates increases in cerebral perfusion during cognitive stimulation (Szabo *et al.* 2011), it seems likely that the capacity to increase cerebral perfusion during cognitive activation is impaired by hyperthermia. Therefore, the purpose of this study was to test the hypothesis that hyperthermia attenuates increases in cerebral perfusion during a cognitive task.

Methods

Subjects

Twenty-one healthy, physically active volunteers (13 men) participated in this study. The subject characteristics were as follows (means \pm SD): age, 29 ± 7 years; height, 175 ± 13 cm; weight, 70.4 ± 15.3 kg; and body surface area, 1.9 ± 0.3 m². Nineteen of the subjects identified themselves as being right handed (Oldfield, 1971). All subjects were non-smokers, not taking medications, free of any known cardiovascular, metabolic, neurological or psychological diseases and had normal or corrected-to-normal vision. Each subject was fully informed of the experimental procedures and possible risks before giving informed written consent. This protocol was approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital of Dallas, and all procedures conformed to the standards set by the Declaration of Helsinki. Subjects arrived at the laboratory euhydrated (confirmed via a urine specific gravity <1.025) and having refrained from strenuous exercise, alcohol and caffeine for a period of 24 h.

Instrumentation and measurements

Approximately 90 min prior to experimental testing, each subject swallowed a telemetry pill (HQ Inc., Palmetto, FL, USA) for the measurement of intestinal temperature. Mean skin temperature was measured as the weighted average of six thermocouples attached to the skin. Body temperature was controlled via a water-perfused, tube-lined suit (Med-Eng, Ottawa, Ontario, Canada) that covered the entire body except the head, hands, one forearm and the feet. Heart rate was continually recorded from an electrocardiogram (HP Patient Monitor; Agilent, Santa Clara, CA, USA) interfaced with a cardiometer (CWE, Ardmore, PA, USA). Beat-to-beat arterial pressure was continuously measured via the Penaz method (Finometer Pro; FMS, Amsterdam, The Netherlands), which was confirmed

intermittently via auscultation of the brachial artery by electrospigmomanometry (Tango+; SunTech, Raleigh, NC, USA). Throughout the protocol, the subjects wore a nose-clip and breathed through a mouthpiece. Expired gases were measured for the partial pressure of end-tidal carbon dioxide (P_{ET,CO_2} ; VitalCap Capnograph Monitor; Oridion, Needham, MA, USA), which served as a surrogate for arterial carbon dioxide tension (Brothers *et al.* 2011).

nBack test—The nBack test was the cognitive stimulus. This test is a standardized test of working memory (Braver *et al.* 1997; Owen *et al.* 2005), can be graded in difficulty (Braver *et al.* 1997; Ocon *et al.* 2012; Stewart *et al.* 2012) and is relatively short, minimizing internal (intestinal) body temperature elevations during test administration. The nBack test was administered using commercially available software (NTT Systems Inc., Toronto, Ontario, Canada) in a manner that has been described in detail previously (Braver *et al.* 1997; Ocon *et al.* 2012; Stewart *et al.* 2012). During the test, subjects monitored a series of letters and were instructed to respond whenever a stimulus was presented that matched the one presented ‘n’ trials previously, where ‘n’ is the specified ‘nBack level’ (Owen *et al.* 2005). This test consisted of four levels, i.e. 1, 2, 3 and 4 Back, with 1 Back being the easiest condition and 4 Back being the most challenging. The test was completed five times, the first three being practice sessions (avoiding a potential learning effect; Stewart *et al.* 2012 and see Results of present study) and the final two were experimental. The order of the nBack level (i.e. 1, 2, 3 or 4 Back) was randomized, with 20 s between each level. The stimulus duration was 0.5 s and the interstimulus duration 2.5 s. The total duration of each nBack level was 68–75 s, which was dependent upon the nBack level (1 Back being the shortest and 4 Back the longest). There were 10 ‘targets’ in each nBack level, and all inputs were made with the right hand. nBack test responses were made by pressing the spacebar on a keyboard (Black Widow; Razer, San Diego, CA, USA) placed to the right side of the body. The same keyboard was used in all trials, which recorded responses with a 1 ms response latency. nBack performance data are reported as the percentage of correct responses (i.e. percentage correct = number of correct responses/total number of possible responses \times 100).

Cerebral perfusion—Cerebral blood flow was quantified using transcranial Doppler (Duschek & Schandry, 2003; Willie *et al.* 2011a) from bilateral insonation of the middle cerebral arteries. Transcranial Doppler provides a valid and reliable index of time-dependent changes in cerebral blood velocity (Duschek & Schandry, 2003; Willie *et al.* 2011a). The middle cerebral artery was chosen because it supplies ~80% of the blood flow to each hemisphere (Stroobant & Vingerhoets, 2000), and given its responsiveness to tests of working memory (Cupini *et al.* 1996; Sorond *et al.* 2011; Ocon *et al.* 2012; Stewart *et al.* 2012) and hyperthermia (Wilson *et al.* 2006; Fujii *et al.* 2008; Brothers *et al.* 2009; Nelson *et al.* 2011). Middle cerebral artery blood velocity (MCA V) was measured by adjusting a 2 MHz Doppler probe (Multi-flow; DWL Elektronische Systeme, Singen, Germany) over the temporal windows, using search techniques previously described (Aaslid *et al.* 1982; Willie *et al.* 2011a). Once optimal signals were identified, the probes were secured in place using a headband. Peak systolic, diastolic and (integrated) mean blood velocities were extracted over each cardiac cycle. Mean middle cerebral artery blood velocities (MCA V_{mean}) were used in the analysis, given that this value is highly correlated with the volume of blood flowing through a vessel (Duschek & Schandry, 2003). The MCA V_{mean} did not lateralize at any time

(lowest P value = 0.331), and therefore the data presented represent average responses from both temporal windows (e.g. Stewart *et al.* 2012).

Experimental protocol

Following instrumentation, subjects rested quietly in the supine position while normothermic water (34°C) perfused the suit. During this time, the subjects underwent three practice tests (~20 min in total duration). This was followed by 5 min of quiet rest, with eyes open, with the last 60 s recorded as normothermic baseline. This resting period transitioned into normothermic nBack testing. The nBack test was presented on a standard computer monitor suspended a comfortable distance overhead, allowing the subjects to remain supine throughout the experiment. During all nBack testing, the laboratory was quiet and the lights were dimmed. Following completion of the normothermic nBack test battery, the subjects underwent whole-body passive heat stress by perfusing 49°C water through the suit. This heat stress continued until intestinal temperature was elevated by ~1.3°C. Upon the attainment of this hyperthermia, a 5 min period of quiet rest was undertaken, with eyes open, during the last 60 s of which hyperthermic baseline data were collected. This baseline period transitioned into hyperthermic nBack testing, which was followed by whole-body cooling and the restoration of normothermia. The subjects were not allowed to drink at any time during the experimental procedures.

Data analysis

Thermal and haemodynamic data were sampled at 50 Hz via a data acquisition system (Biopac System, Santa Barbara, CA, USA). During each nBack level, MCA V_{mean} data were averaged in 1 s bins, starting 5 s immediately preceding each nBack level. These data were analysed using three distinct, but commonly employed, approaches. First, changes in cerebral perfusion during cognitive activation were calculated as the percentage change in MCA V_{mean} ($\frac{\text{MCA } V_{\text{mean}} - \text{MCA } V_{\text{mean}}}{\text{MCA } V_{\text{mean}}}$) from baseline, as done previously (e.g. Sorond *et al.* 2008; Matteis *et al.* 2009; Sorond *et al.* 2011; Szabo *et al.* 2011; Ocon *et al.* 2012). Baseline was defined as the average MCA V_{mean} during the 5 s period preceding each nBack level (Szabo *et al.* 2011). These data were analysed through 65 s for each nBack level. Second, given the expected (and confirmed; see Results) time-dependent increases in MCA V_{mean} during each nBack level, area-under-the-curve (AUC) analysis was also employed to discern the extent of the changes occurring over time (Pruessner *et al.* 2003). Third, cerebral blood velocity dynamics during cognitive activation were evaluated by analysing the peak MCA V_{mean} response to each nBack level and the time at which this peak occurred (Szabo *et al.* 2011; Willie *et al.* 2011*b*). These analyses were also undertaken for mean arterial pressure (MAP) and $P_{\text{ET,CO}_2}$, because these factors can independently modulate cerebral blood velocity during cognitive activation (Moody *et al.* 2005; Panerai *et al.* 2005).

Statistical analysis

Differences between the normothermic and hyperthermic baseline periods were identified using Student's paired t tests. All other data were analysed using repeated measures ANOVA. These data were assessed for approximation to a normal distribution and sphericity, and no corrections were necessary. When the ANOVAs revealed a significant F test, *post hoc* pairwise comparisons were made, incorporating a Bonferroni adjustment. A

a priori linear relationships between dependent variables were evaluated using Pearson product-moment correlation analysis. To confirm that a learning effect from repeated nBack testing was minimized, within-subject coefficients of variation were calculated to identify nBack performance variability between the nBack practice trials and experimental nBack testing. Data were analysed using SigmaPlot (v12; Systat Software Inc., Chicago, IL, USA) with *a priori* statistical significance set at $P < 0.05$. All data are reported as means \pm SD.

Results

nBack practice

The practice nBack testing was effective in minimizing a learning effect. For all levels of the nBack assessment, nBack performance was lowest ($P = 0.027$) during the first practice trial, but improved thereafter such that there were no differences between nBack performance in the second ($P = 0.236$) and third practice trials ($P = 0.998$) relative to the normothermic experimental nBack testing. Within-subject coefficients of variation in nBack performance for all levels of nBack were similar between the second and third (final) nBack practice tests ($P = 0.998$) and between the third nBack practice test and the normothermic experimental nBack test ($P = 0.998$). Mean within-subject coefficients of variation between the third nBack practice test and the normothermic experimental nBack test for each nBack level were as follows: 1 Back, $4 \pm 8\%$; 2 Back, $7 \pm 7\%$; 3 Back, $11 \pm 9\%$; and 4 Back, $7 \pm 5\%$.

Baseline thermal and haemodynamic data

Hyperthermia was characterized by $\sim 5.0^\circ\text{C}$ elevation ($P < 0.001$) in mean skin temperature, a $\sim 1.3^\circ\text{C}$ increase ($P < 0.001$) in intestinal temperature, reductions ($P < 0.020$) in right and left diastolic MCA V and MCA V_{mean} , MAP and $P_{\text{ET,CO}_2}$, and elevated ($P < 0.001$) heart rates. Systolic MCA V was preserved ($P = 0.380$) during hyperthermia (Table 1).

nBack test responses

nBack performance decreased ($P < 0.001$) with increasing nBack level. However, there was no effect ($P = 0.276$) of body temperature on test performance (Fig. 1). Mean within-subject coefficients of variation between the normothermic and hyperthermic experimental nBack testing were as follows: 1 Back, $4 \pm 8\%$; 2 Back, $5 \pm 7\%$; 3 Back, $11 \pm 11\%$; and 4 Back, $8 \pm 6\%$; these values were similar ($P = 0.998$) to those occurring between the final nBack practice test and the normothermic experimental nBack test (see above section '*nBack Practice*'). Increases in intestinal temperature ($P = 0.201$), mean skin temperature ($P = 0.639$) and heart rate ($P = 0.840$) remained stable (from baseline) during nBack testing. Both MAP (Fig. 2) and $P_{\text{ET,CO}_2}$ (Fig. 3) were reduced ($P < 0.010$) by hyperthermia. Irrespective of thermal condition ($P = 0.381$), changes in MAP remained stable ($P = 0.051$) throughout nBack testing, except during 4 Back ($P = 0.014$; Fig. 2). Changes in $P_{\text{ET,CO}_2}$ during nBack testing were also similar ($P = 0.793$) between thermal conditions (Fig. 3). Area-under-the-curve analysis indicated that MAP did not differentiate ($P = 0.996$) between nBack levels, but MAP was generally greater during normothermia (Table 2). Area-under-the-curve analysis for $P_{\text{ET,CO}_2}$ indicated the responses were quite variable (Table 2), and therefore changes over time during each nBack level were negligible and thus were not differentially affected by body temperature ($P = 0.864$) or nBack level ($P = 0.242$; Table 2). This AUC

analysis corroborates the MAP and P_{ET,CO_2} time series analysis (Figs 2 and 3) and collectively indicates that changes in MAP and P_{ET,CO_2} during nBack testing were minimally affected by nBack levels or thermal conditions.

Cerebral blood velocity during nBack testing

Given that heat stress itself decreased MCA V_{mean} (Table 1), MCA V_{mean} was lower ($P < 0.001$) throughout all nBack levels during hyperthermia (Fig. 4). Notably, the magnitude of the increase in MCA V_{mean} (MCA V_{mean}) during nBack testing was similar ($P = 0.608$) between thermal conditions (Fig. 4). This finding was confirmed when evaluated using the AUC analysis (Table 2), such that there was no effect of nBack level ($P = 0.419$) or body temperature ($P = 0.947$) on the magnitude of the increase in MCA V_{mean} (Table 2). The peak MCA V_{mean} response to each nBack level was higher ($P < 0.001$) during normothermia, but the time at which this peak occurred ($P = 0.745$) and the relative change (i.e. MCA V_{mean}) from baseline ($P = 0.180$) were independent of changes in body temperature (Table 3).

Correlation analysis

No significant relationships between MCA V_{mean} AUC and nBack performance were observed when evaluated during normothermia ($r^2 = 0.0025$, $P = 0.653$), hyperthermia ($r^2 = 0.0018$, $P = 0.699$) or combined normothermia and hyperthermia ($r^2 = 0.0000$, $P = 0.937$). There was a very weak but significant relationship between MCA V_{mean} AUC and MAP AUC during hyperthermia ($r^2 = 0.0600$, $P = 0.034$), but not during normothermia ($r^2 = 0.0185$, $P = 0.242$), while MCA V_{mean} AUC and P_{ET,CO_2} AUC were found to be correlated weakly during both normothermia ($r^2 = 0.0462$, $P = 0.049$) and hyperthermia ($r^2 = 0.2510$, $P < 0.001$).

Discussion

The novel finding of this study is that the increase in cerebral perfusion during cognitive activation is well preserved during hyperthermia; therefore, we reject our hypothesis. These data specifically demonstrate that hyperthermia-induced reductions in MCA V_{mean} , MAP and P_{ET,CO_2} (Table 1 and Figs 2 and 3) do not alter subsequent increases in MCA V_{mean} during graded nBack tests. This conclusion was found to be consistent when expressed as: (i) average changes occurring over time (Fig. 4); (ii) the accumulated magnitude of these time-dependent changes, i.e. AUC (Table 2); or (iii) the dynamics of the peak responses (Table 3). Collectively, these findings indicate that the capacity to increase cerebral perfusion in response to a cognitive task involving processes of working memory is unaffected by increases in mean skin and internal (intestinal) body temperatures at the levels achieved in the present study.

Cognitive activation and cerebral blood velocity during hyperthermia

Chronic reductions in baseline cerebral perfusion (i.e. by 10–20%) impair subsequent increases in cerebral perfusion during a cognitive challenge in healthy older individuals (Sorond *et al.* 2008) and in patients with essential hypotension (Duschek & Schandry, 2004). Based upon those observations, we hypothesized that a reduction in (baseline) cerebral perfusion by ~14% during hyperthermia (Table 1) would attenuate subsequent increases in

cerebral perfusion during a test of working memory. On the contrary, such coupling was remarkably preserved (Fig. 4 and Tables 2 and 3), despite additional hyperthermia-induced reductions in MAP and P_{ET,CO_2} (Table 1 and Figs 2 and 3). Importantly, hyperthermia had little influence on P_{ET,CO_2} and MAP during nBack testing (Table 2 and Figs 2 and 3). As such, changes in MAP during nBack testing accounted for no more than 6% of the variance associated with cognitive-induced changes in MCA V_{mean} . From these findings, we are confident that the observed increases in MCA V_{mean} were due to reductions in cerebral vascular resistance (as opposed to increases in perfusion pressure; i.e. Poiseuille's Law), the former of which is likely to have occurred secondary to an increase in metabolic and neuronal demand. Importantly, these data indicate that the magnitude of the change in cerebral vascular resistance during the nBack procedures is independent of increases in body temperature. This observation is consistent with previous findings from our laboratory demonstrating that hyperthermia has little effect on dynamic cerebral autoregulation (Low *et al.* 2009) or cerebrovascular responsiveness to carbon dioxide (Low *et al.* 2008), which are factors that are proposed to be mediated by the same physiological mechanisms as those governing changes in cerebral haemodynamics during cognitive activation (Rosengarten *et al.* 2001).

Hypocapnia independently impairs increases in cerebral perfusion during cognitive stimulation (Szabo *et al.* 2011). Therefore, our findings that hyperthermia, which was coupled with mild hypocapnia (Tables 1 and 2 and Fig. 3), did not alter cognitive-induced changes in MCA V_{mean} (Fig. 4 and Tables 2 and 3) were unexpected. The rationale for these apparently contradictory findings is probably threefold. First, the magnitude of hypocapnia during hyperthermia in the present study was appreciably smaller than that imposed by Szabo *et al.* (2011; ~4 versus ~12 mmHg reductions). Second, the cognitive stimulus in the present study involved working memory, which is in contrast to the reading stimulus used by Szabo *et al.* (2011). Third, different cerebral arteries were assessed between these studies. Given its sensitivity to visual stimulation (Aaslid, 1987), Szabo *et al.* (2011) measured blood velocity in the posterior cerebral artery, while in the present study we assessed velocity in the middle cerebral artery because it is responsive to tests of working memory (Cupini *et al.* 1996; Sorond *et al.* 2008, 2011; Ocon *et al.* 2012; Stewart *et al.* 2012). To our knowledge, the effect of hypocapnia on increases in cerebral perfusion during cognitive activation in different cerebral vessels remains uncertain. However, given recent findings indicating regional variations in cerebral chemosensitivity (Sato *et al.* 2012; Willie *et al.* 2012), such differences appear likely. Notably, correlation analyses of the present data indicated that changes in P_{ET,CO_2} during cognitive activation were (very) weakly associated with changes in MCA V_{mean} during both normothermia and hyperthermia. This corroborates previous work, indicating that changes in arterial carbon dioxide tension play no more than a minor role in modulating cerebral perfusion during cognitive activation (Moody *et al.* 2005; Panerai *et al.* 2005).

Cerebral perfusion and cognitive performance during hyperthermia

We anticipated that nBack performance would deteriorate during hyperthermia and that the magnitude of this deterioration would be related to the hypothesized attenuated increases in MCA V_{mean} . This expectation was predicated on the previous findings indicating that the

capability to increase cerebral perfusion during cognitive activation is positively related to task performance (Duschek & Schandry, 2006; Matteis *et al.* 2009; Sorond *et al.* 2011; Stewart *et al.* 2012) and that many aspects of cognitive function (e.g. attention, executive functioning and memory) are impaired during hyperthermia (Wilkinson *et al.* 1964; Hocking *et al.* 2001; McMorris *et al.* 2006; Racinais *et al.* 2008; Gaoua *et al.* 2011*a,b*, 2012*a,b*). However, we found no effect of hyperthermia on nBack performance (Fig. 1), and thus it is not surprising that there were no relationships between nBack performance and the increase in MCA V_{mean} . The rationale for an absence of an effect of hyperthermia on nBack performance probably lies with the nBack protocol used in the present study. For instance, the impact of hyperthermia on cognitive function is largely task dependent (Hancock & Vasmatazidis, 2003). That is, those cognitive tests involving greater neuronal resources are impaired to a greater extent than less demanding tasks (Hocking *et al.* 2001; Gaoua, 2010, 2012*b*). The nBack test is a test of working memory (Owen *et al.* 2005), an aspect of cognition that demands a relatively large portion of the neuronal resources (Hocking *et al.* 2001). Thus, we anticipated that nBack test performance would be impaired by hyperthermia. Yet, despite the deterioration of nBack test performance with increasing nBack levels, hyperthermia did not affect test performance (Fig. 1). Although it is clear that the nBack test provided a challenging cognitive stimulus, it is speculated that the nBack protocol did not elicit a sufficient neuronal ‘overload’ necessary for hyperthermia-induced decrements in working memory performance (e.g. Gaoua *et al.* 2012*b*). Given that increases in cerebral neuronal activity are accurately reflected by increases in cerebral blood velocity (Zaletel *et al.* 2004; Rosengarten *et al.* 2006), our MCA V_{mean} data appear to support this conjecture (Fig. 4 and Tables 2 and 3).

Methodological considerations

We used transcranial Doppler to quantify MCA V , given that this technique allows for convenient, continuous and non-invasive measurement of blood velocities in the cerebral arteries at a high temporal resolution (Stroobant & Vingerhoets, 2000; Duschek & Schandry, 2003; Willie *et al.* 2011*a*). It must be acknowledged that if the diameter of the insonated artery changes, blood velocity may not reflect changes in blood flow. Notably, however, the diameter of the middle cerebral artery is unaffected by moderate carbon dioxide and arterial pressure perturbations (Giller *et al.* 1993; Serrador *et al.* 2000).

A related consideration is the cerebral arteries that we chose to insonate. We monitored MCA V given its responsiveness to tests of working memory (Cupini *et al.* 1996); specifically, the nBack test (Sorond *et al.* 2011; Ocon *et al.* 2012; Stewart *et al.* 2012) and hyperthermia (Wilson *et al.* 2006; Fujii *et al.* 2008; Brothers *et al.* 2009; Nelson *et al.* 2011). However, it could be argued that the anterior cerebral artery is a more appropriate vessel to insonate because it provides more direct perfusion of the frontal lobes (Rosengarten *et al.* 2012), which are vital in the execution of tasks of working memory (Owen *et al.* 1990; Fletcher & Henson, 2001; Baldo & Shimamura, 2002). Relative to the middle cerebral artery, however, insonation of the anterior cerebral artery can be challenging due to its relatively small size (Willie *et al.* 2011*a*). Therefore, given that changes in MCA V during executive functioning tasks, which involve many aspects of working memory (Drag & Bieliauskas, 2010), reflect blood velocity changes in the anterior cerebral artery

(Schuepbach *et al.* 2002, 2007), we deemed the insonation of the middle cerebral artery appropriate. Nevertheless, the possibility remains that hyperthermia modified the increase in perfusion during cognitive activation in other, non-insonated cerebral arteries.

Hyperthermia influences cerebral metabolic (Nunneley *et al.* 2002; Nybo *et al.* 2002) and neural responses (Dubois *et al.* 1980, 1981). To our knowledge, however, the effects of hyperthermia on metabolic and neural responses to a cognitive stimulus remain uncertain. Thus, in the present study we assumed that the magnitude of cerebral metabolic and neural demand at a given nBack level is unaffected by hyperthermia.

Perspectives and future directions

The findings of this study extend previous work from our laboratory indicating that cerebrovascular responsiveness is generally unaffected by hyperthermia. Specifically, dynamic cerebral autoregulation (Low *et al.* 2009), carbon dioxide reactivity (Low *et al.* 2008) and now cerebrovascular responsiveness to a cognitive stimulus (Fig. 4 and Tables 2 and 3) are all maintained irrespective of increases in body temperature and associated reductions in cerebral perfusion. It is notable, however, that the findings of this study pertain only to situations involving aspects of working memory, the performance of which was unaffected by hyperthermia.

Conclusions

The present study demonstrates that hyperthermia, and the accompanying moderate reductions in cerebral blood velocity, arterial pressure and end-tidal carbon dioxide tension, do not alter the capability to increase cerebral blood velocity during a cognitive challenge involving working memory. These findings confirm that hyperthermia has little influence on cerebrovascular reactivity.

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New Findings

- What is the central question of this study?

Decreases in baseline cerebral perfusion impair the capacity to increase cerebral perfusion during cognitive activation. Hyperthermia reduces baseline cerebral perfusion, but it remains unknown whether hyperthermia also impairs the increase in cerebral perfusion during the execution of a cognitive task.
- What is the main finding and its importance?

This study shows that hyperthermia does not alter the increase in cerebral perfusion during a cognitive task. These findings have implications for individuals who are frequently exposed to heat stress in concert with a cognitive challenge.

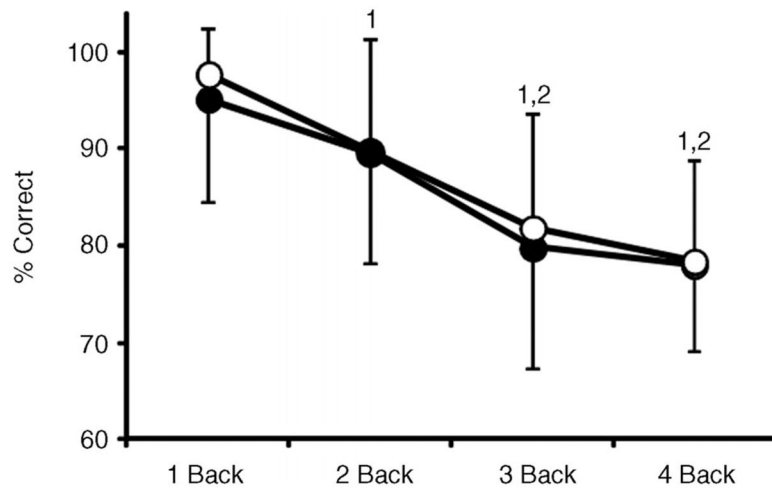


Figure 1. nBack performance expressed as a percentage of correct responses (% correct) across levels of nBack (mean \pm SD) in normothermia (open circles) and hyperthermia (filled circles) '1' and '2' indicate significant difference ($P < 0.004$) from 1 Back and 2 Back tests, respectively.

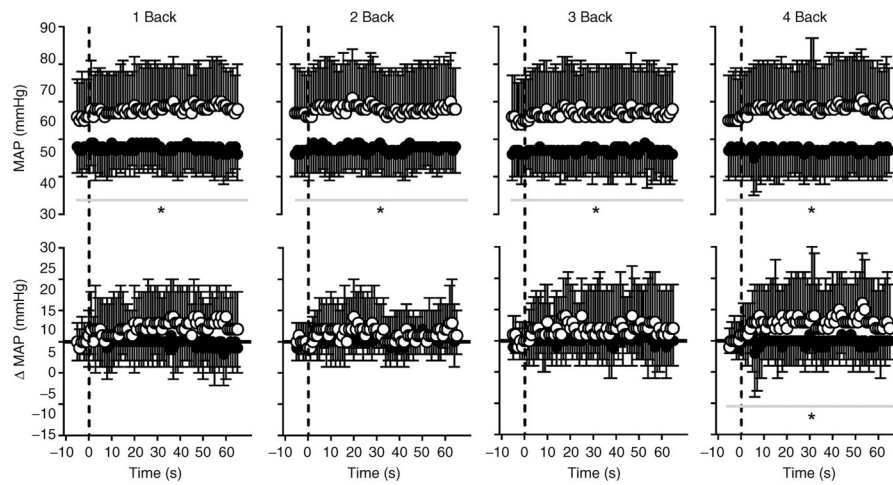


Figure 2. Mean arterial pressure (MAP) expressed as absolute values (top panels) and as the change from baseline (bottom panels; Δ MAP) over time during 1 Back, 2 Back, 3 Back and 4 Back tests (means \pm SD) in normothermia (open circles) and hyperthermia (filled circles). The vertical dashed line indicates the start of each nBack test; the horizontal continuous black line (in Δ MAP graphs) indicates zero (or no change). *Significantly different ($P < 0.014$) from normothermia. Owing to the large number of potential comparisons, pairwise comparisons were not conducted in this analysis.

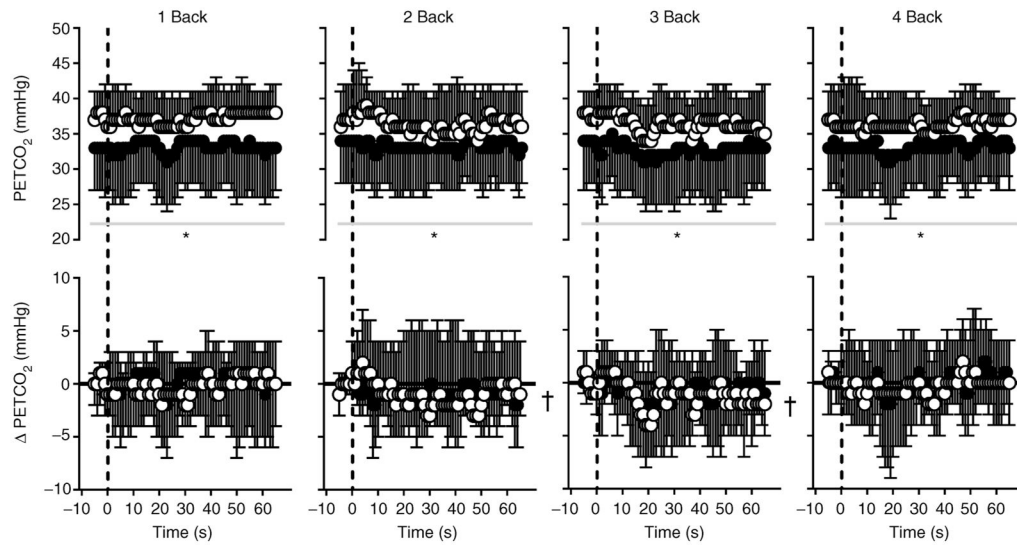


Figure 3. End-tidal carbon dioxide tension (P_{ET,CO_2}) expressed as absolute values (top panels) and as the change from baseline (bottom panels; P_{ET,CO_2}) over time during 1 Back, 2 Back, 3 Back and 4 Back tests (means \pm SD) in normothermia (open circles) and hyperthermia (filled circles)

The vertical dashed line indicates the start of each nBack test; the horizontal continuous black line (in P_{ET,CO_2} graphs) indicates zero (or no change). *Significantly different ($P < 0.019$) from normothermia; and †significant ($P < 0.040$) main effect of time. Owing to the large number of potential comparisons, pairwise comparisons were not conducted in this analysis.

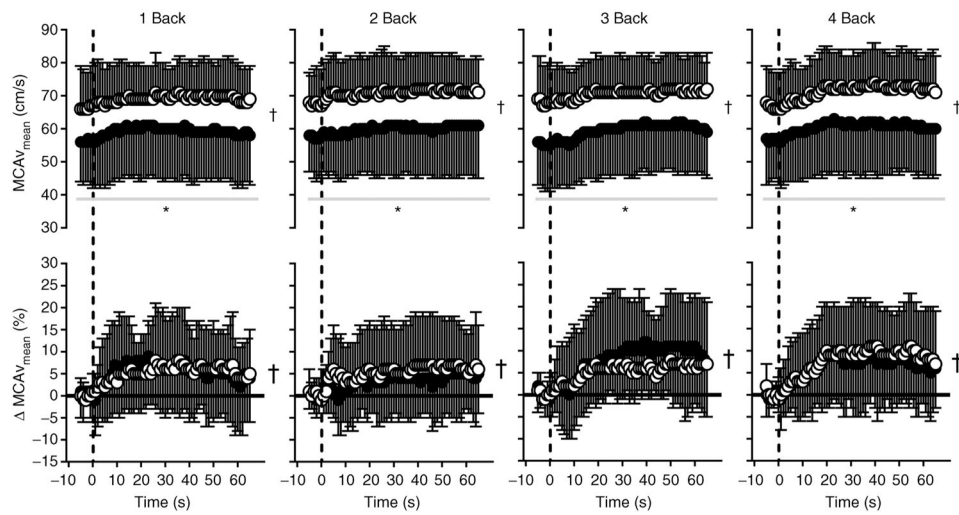


Figure 4. Mean middle cerebral artery blood velocity ($MCAV_{\text{mean}}$) expressed as absolute values (top panels) and as the percentage change from baseline (bottom panels; $\Delta MCAV_{\text{mean}}$) over time during 1 Back, 2 Back, 3 Back and 4 Back tests (means \pm SD) in normothermia (open circles) and hyperthermia (filled circles)

The vertical dashed line indicates the start of each nBack test; the horizontal continuous black line (in $MCAV_{\text{mean}}$ graphs) indicates zero (or no change). *Significantly different ($P < 0.001$) from normothermia; and †significant ($P < 0.001$) main effect of time. Owing to the large number of potential comparisons, pairwise comparisons were not conducted in this analysis.

Table 1

Normothermic and hyperthermic baselines

Parameter	Normothermia	Hyperthermia
Mean skin temperature (°C)	34.4 ± 0.5	39.4 ± 1.0 *
Intestinal temperature (°C)	36.9 ± 0.3	38.3 ± 0.3 *
Right MCA <i>V</i> (cm s ⁻¹)		
Peak systolic	97 ± 12	97 ± 20
End diastolic	52 ± 7	43 ± 10 *
Mean	70 ± 10	61 ± 14 *
Left MCA <i>V</i> (cm s ⁻¹)		
Peak systolic	94 ± 16	90 ± 25
End diastolic	50 ± 9	41 ± 13 *
Mean	68 ± 11	58 ± 17 *
MAP (mmHg)	76 ± 11	66 ± 7 *
<i>P</i> _{ET,CO₂} (mmHg)	38 ± 3	34 ± 5 *
Heart rate (beats min ⁻¹)	56 ± 9	90 ± 14 *

Values are means ± SD. Abbreviations: MAP, mean arterial blood pressure; MCA *V*, middle cerebral artery blood velocity; and *P*_{ET,CO₂}, partial pressure of end-tidal carbon dioxide.

* Significantly different from normothermia (*P* < 0.020).

Area-under-the-curve analysis

Table 2

Parameter	1 Back		2 Back		3 Back		4 Back	
	Normothermia	Hyperthermia	Normothermia	Hyperthermia	Normothermia	Hyperthermia	Normothermia	Hyperthermia
MCA V_{mean} AUC (a.u.)	4562 ± 655	3916 ± 981*	4678 ± 681	3956 ± 927*	4661 ± 649	3935 ± 913*	4713 ± 668	4000 ± 962*
MCA V_{mean} AUC (a.u.)	348 ± 533	356 ± 584	348 ± 552	230 ± 476	348 ± 845	513 ± 570	507 ± 585	427 ± 564
MAP AUC (a.u.)	5152 ± 691	4469 ± 429*	5148 ± 743	4454 ± 410*	5067 ± 771	4420 ± 419*	5161 ± 779	4431 ± 469*
MAP AUC (a.u.)	217 ± 334	20 ± 293*	104 ± 227	82 ± 108	160 ± 497	49 ± 210	193 ± 323	19 ± 204*
P_{ETCO_2} AUC (a.u.)	2452 ± 199	2189 ± 384*	2392 ± 199	2195 ± 350*	2399 ± 193	2165 ± 383*	2387 ± 206	2189 ± 344*
P_{ETCO_2} AUC (a.u.)	-18 ± 317	65 ± 787	-58 ± 861	-138 ± 363	-191 ± 387	-161 ± 465	2 ± 615	30 ± 508

Values are means ± SD. Abbreviations: a.u., arbitrary units; AUC, area under the curve; MAP, mean arterial pressure; MAP, percentage change in mean arterial pressure; MCA V_{mean} , mean middle cerebral artery blood velocity; MCA V_{mean} , percentage change in mean middle cerebral artery blood velocity; P_{ETCO_2} , partial pressure of end-tidal CO₂; and P_{ETCO_2} , percentage change in the partial pressure of end-tidal CO₂.

* Significantly different from normothermia ($P < 0.01$).

Table 3

Activation–flow coupling dynamics of MCA V_{mean}

Parameter	Normothermia				Hyperthermia			
	1 Back	2 Back	3 Back	4 Back	1 Back	2 Back	3 Back	4 Back
Baseline (cm s^{-1})	66 ± 12	68 ± 10	68 ± 12	67 ± 11	56 ± 13*	58 ± 12*	56 ± 13*	57 ± 13*
Peak (cm s^{-1})	77 ± 12 [†]	80 ± 12 [†]	78 ± 11 [†]	79 ± 12 [†]	65 ± 16 ^{*†}	67 ± 16 ^{*†}	67 ± 14 ^{*†}	67 ± 16 ^{*†}
Change (%)	18 ± 11	19 ± 11	16 ± 15	19 ± 11	17 ± 11	15 ± 7	22 ± 14	17 ± 11
Time (s)	31 ± 18	28 ± 18	31 ± 19	38 ± 15	28 ± 19	33 ± 22	36 ± 19	29 ± 20

Values are means ± SD. Abbreviations: MCA V_{mean} , mean middle cerebral artery blood velocity; Baseline, average MCA V_{mean} during 5 s prior to initiation of nBack; Peak, highest MCA V_{mean} during nBack; Change, Peak as a percentage change from Baseline; and Time, time at which Peak occurred.

* Significantly different from normothermia ($P < 0.001$);

[†] significantly different from Baseline ($P < 0.001$).