International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: informahealthcare.com/journals/ihyt20

Hyperthermic effects on behavior

William C. Wetsel

To cite this article: William C. Wetsel (2011) Hyperthermic effects on behavior, International Journal of Hyperthermia, 27:4, 353-373, DOI: 10.3109/02656736.2010.550905

To link to this article: https://doi.org/10.3109/02656736.2010.550905

Int. J. Hyperthermia, June 2011; 27(4): 353–373

informa
healthcare

Hyperthermic effects on behavior

WILLIAM C. WETSEL

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710 USA

(Received 1 December 2010; Accepted 22 December 2010)

Abstract

This review focuses upon the past 8 years of research on hyperthermic effects on behavior. Heat stress and heat stoke become severe conditions when body temperatures exceed 40°C as this can lead to delirium, convulsions, coma, and death. The animal literature indicates that hyperthermia can increase glutamatergic and decrease GABAergic neurotransmission. Interestingly, μ-opiate receptor antagonists can attenuate the morphological and biochemical changes in brain, as well as, ameliorate some behavioral deficits induced by heart stress. In humans, heat stress can produce detrimental effects on motor and cognitive performance. Since most cognitive tasks require a motor response, some cognitive deficiencies may be attributed to decreased motor performance. Although hyperthermia may exert more deleterious effects on complex than simple cognitive tasks, systematic studies are needed to examine the effects of different levels and durations of hyperthermia (irrespective of dehydration) on cognition. Additionally, body temperatures should be carefully monitored where controls are run for baseline or brief exposures to a hyperthermic environment.

Acute radiofrequency exposure can disrupt behavior when body temperatures increase >1°C with whole body SAR between 3.2–8.4 W/kg and time-averaged power densities at 8–140 mW/cm^2. Effects of lower levels of radiation are conflicting and some experiments fail to replicate even with the original investigators. This suggests either that brief exposure to the radiation is at a threshold where some individuals are affected while others are not, or that these levels are innocuous. Nevertheless, thermal changes appear to account for almost all of the behavioral effects reported.

Keywords: *Hyperthermia, radiofrequency radiation, behavior, pain, cognition, motor responses, emotionality*

Introduction

Maintenance of body temperature within a specific range is essential for mammalian survival. Mammals defend their body temperatures through numerous physiological and behavioral mechanisms to support ongoing biochemical processes. Innate acute nocifensive behaviors allow the organism to escape from environmental conditions of intense cold or heat so that tissue damage, morbidity, or mortality do not occur. Nevertheless, brief exposure to intense temperature changes is known to modify behavior. The present manuscript reviews the literature over the past 8 years to examine effects of hyperthermia and radiofrequency exposure on behavior.

Pain responses to heat

It has long been known that humans and animals are sensitive to thermal stimulation. In fact, in animals the tail-flick and hot-plate tests have long been used to assess nociceptive thermal responses. The tail-flick test relies primarily upon spinal reflexes, whereby hot-plate responses require responses from higher centers of the central nervous system [1–3]. Stress can induce analgesia by restraint, cold-water exposure, and foot-shock [4–6]. Since analgesia has such a pronounced effect on the tail-flick and hot-plate tests, these tasks are often used to assess tolerance to opiates and naloxone or to naltrexone-precipitated withdrawal [7]. Many of these responses are medi-

Correspondence: William C. Wetsel, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 103203, 0354 Sands Building, Research Drive, Durham, NC 27710 USA. Tel: 919-684-4567. Fax: 919-684-3071. E-mail: wetse001@mc.duke.edu

ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.3109/02656736.2010.550905

ated by μ opiate receptors. In this respect, μ agonists are less effective with high intensity than with low intensity thermal stimuli [8]. Additionally, lower intensity stimuli activate C-fiber nociceptors, while higher thermal stimuli activate Aδ and other nociceptive systems [9–11]. In animals, responses on these tests can be influenced by age, sex, phase of estrus cycle, and developmental experience [12–14]. There is also some evidence for ethnic and gender differences in humans in response to thermal stimuli [15–16]. Interestingly, peripheral temperature has been reported to affect both tail-flick and hot-plate responses [17–19].

An analog of the tail-flick test for rodents has been developed as the finger withdrawal test for humans [20]. Greenwald and Johanson [21] used this test to evaluate thermal pain sensitivity in 10 subjects. A repeated measures crossover design was used where the subject's left and right fingers were exposed individually to radiant temperatures of 42.2°C, 42.8°C, 43.4°C, 44.4°C, 46.7°C, 48.9°C, and 52.2°C for up to 20 seconds. Temperature was measured by a thermistor attached to the middle finger of one hand – trials were initiated only when finger temperature was between 31.1 and 33.3°C. Subjects were tested over 4 session days where the intensities of the thermal stimuli were administered in a randomized order. On separate days, subjects were told to remove their finger from the heat source according to four different instructions: sensory – withdraw the finger when heat is first felt, affective – withdraw the finger when the heat is unpleasant, pain – withdraw the finger when pain is felt, and intolerance – withdraw the finger when pain is no longer tolerated. As may be anticipated, withdrawal latencies declined with increased thermal stimulation. Latencies were shortest for the ''sensory'' instructions, most prolonged for ''intolerance,'' with no distinctions between the ''affective'' and ''pain'' instructions. An intriguing aspect of the study is that the left finger was more sensitive to thermal stimulation than the right. Unfortunately, no information was provided for handedness of the subjects. Although these results indicate that instruction set can greatly influence human responses to thermal nocioceptive stimuli, other investigators have found at least prior experience does not affect thermal pain thresholds [22]. Therefore, additional studies are warranted to determine under what circumstances instruction set can affect perception and responses to thermal stimuli.

Overview of heat stress effects on behavior

Heat stress and heat stroke become severe conditions when body temperatures exceed 40°C and these circumstances can lead to delirium, convulsions, coma, and death [23]. In fact, up to 50% of the heat stroke patients die and those who survive frequently present with neurological deficits. Hence, conditions that raise core body temperatures can be deleterious to neural function. To protect against increases in body temperature, a variety of mechanisms have been developed. For instance, homeostatic mechanisms responsible for maintaining body temperature include alterations in metabolic rate, autonomic responses such as sweating and vasodilatation, changes in appetite and thirst, alterations in neuroendocrine function particularly as they relate to thyroid, adrenal, and neurohypophyseal responses, and changes in behavior. Since some agencies such as the National Institute for Occupational Safety and Health [24] have been particularly concerned with these effects, the present review will summarize the recent literature of heat stress effects on neural systems and behavior.

Effects of hyperthermia on animal behavior

Changes in body temperature can occur naturally though prolonged exercise, illness-induced fever, and alterations in environmental temperatures. Increases in body temperature can produce a number of different neurological symptoms, as well as, induce seizures even at lower temperatures in susceptible individuals [23]. Febrile seizures are the most common type of seizure in childhood [25–28]. They can lead to hippocampal cell loss in infancy [29] and, although controversial, may promote temporal lobe sclerosis and temporal lobe epilepsy in adults [30–31]. In rodents, hyperthermia alone increases neuronal excitability [32, 33], enhances susceptibility to seizure [34–37], and can exert untoward effects on learning and memory [38]. Parenthetically, recent work has shown that activation of TRPV1 and TRPV4 channels can lead to hippocampal excitation and disinhibition [39–40]. In an animal model of febrile seizure, Mesquita and colleagues [41] exposed 10-day old rats to an environment of 41°C for 30 min (Table I). Importantly, while the investigators state that rectal temperatures were monitored to ensure that core temperatures were similar to those during high fever, the body temperatures were not reported. Behavior was recorded 24 hrs after hyperthermia and 3 months later. The only notable effect observed at 24 hrs was that the hyperthermia-exposed rats opened their eyes 2 days earlier prior to controls; other neurological reflexes appeared normal. At 3 months of age animals were tested in the open field for motor activity, the elevated plus maze for anxiety-like behavior, the forced-swim task for antidepressive-like responses, and the Morris water maze for spatial

Table I. Behavioral effects of hyperthermia in rats.

Animals	Exposure	Effect During Exposure	Behavioral tests	Results	Reference
Male Wistar rats; $n=14$ rats/group	41°C environment for 30 min[a]	Seizure	Neurodevelopmental screen	24 hrs after exposure: Advanced eye opening	[41]
			Open field	At 3 mos: ↓ activity in center of open field	
			Elevated plus maze	At 3 mos: ↓ open arm time	
			Forced swim	At 3 mos: no Δ[b]	
			Morris water maze and reversal	At 3 mos: no Δ[b]	
Wistar rats; $n=5$–7 rats/group	Rectal temperature of 33, 37, or 39°C ± anoxia[c]		Open field	At 5–30 days: ↑ % motor activity with 37 and 39°C, further ↑ anoxia At 45 days: ↑ linear velocity with 39°C	[45]
			Open field + deferoxamine	Normalized behavior	
Male Wistar rats; $N=4$–11 rats/group	Body temperature of 33, 37, or 39°C ± anoxia[d]		Open field	At 4 mos: ↓ motor activity with ↑ temperature, further ↓ anoxia 39°C	[46]
			Open field + deferoxamine	Normalized behavior	
			Elevated plus maze	At 4 mos: no Δ[b] time spent and entries into open arms (trial 1), ↑ with anoxia	
			Elevated plus maze + deferoxamine	Normalized behavior	
			Sudden silence	At 4 mos: ↓ latency to move and ↑ motor activity with ↑ temperature	
			Sudden silence + deferoxamine	At 4 mos: no Δ[b]	
			Telemetry – body temperature rhythm	At 4 mos: no Δ[b]	
			Telemetry – home-cage activity	At 4 mos: ↑ motor activity 33°C prior to plus maze test, no change afterwards	
Male albino Wistar rats[e]; $n=5$–12 rats/group	38°C environment for ½, 1, 2, 3, or 4 hrs	~20% rats died at 4 hrs	Rectal temperature[e]	↑ with duration of heat exposure	[56]
			Salivation[e]	↑ with duration of heat exposure	
			Body weight[e]	↓ at 4 hrs	
			Prostration[e]	↑ at 4 hrs	
			Blood pressure[e]	variable	
			Arterial pH[e]	no Δ[b]	
			PaO_2[e]	↑ at 4 hrs	

(*continued*)

Table 1. Continued.

Animals	Exposure	Effect During Exposure	Behavioral tests	Results	Reference
			$PaCO_2$[e]	↓ at 4 hrs	
			Gastric hemorrhage[e]	↑ with duration of heat exposure	
			Tail flick[e]	no Δ[b]	
			Rotorod[f]	At 3 and 4 hrs: ↓ response	
			Grid walking[f]	At 3 and 4 hrs: ↓ walking and ↑ placement error	
			Inclined plane[f]	At 3 and 4 hrs: ↓ response	
			Foot-printing[f]	At 3 and 4 hrs: ↑ distance and ↓ stride-length	
			Neurochemistry[f]	Variable effects	
			BBB permeability[f,g]	At 4 hrs: ↑ permeability	
			Regional blood flow in brain[f]	At 4 hrs: ↓ flow	
			Brain edema[f]	At 4 hrs: ↑ edema	
			Structural Δ[b,f]	At 4 hrs: structural changes	
			Rectal temperature at 4 hrs + naloxone[e,f]	Attenuated[i]	
			Prostration at 4 hrs + naloxone[e,h]	Attenuated[i]	
			Body weight at 4 hrs + naloxone[e,h]	Attenuated[i]	
			Blood pressure[e,h]	Attenuated[i]	
			Arterial pH[e,h]	Attenuated[i]	
			PaO_2[e,h]	Attenuated[i]	
			$PaCO_2$[e,h]	Attenuated[i]	
			Gastric hemorrhage + naloxone[e,h]	Attenuated[i]	
			Inclined plane + naloxone[f,h]	Normalized behavior	
			Foot-printing + naloxone[f,h]	no Δ[b]	
			Rotorod + naloxone[f,h]	no Δ[b]	
			Grid walking + naloxone[f,h]	Normalized walking, no Δ[b] placement	
			Neurochemistry + naloxone[f,h]	Normalized	
			BBB permeability[f,h]	Attenuated[i]	
			Regional blood flow in brain + naloxone[f,h]	Attenuated[i]	
			Brain edema[f,h]	Attenuated[i]	
			Structural Δ[b,f,h]	Attenuated[i]	

[a]Rats were exposed to hyperthermia at post-natal day 8. Rats were behaviorally tested at post-natal days 8 (before hyperthermia), 12, 14, and 16, and at 3 mos of age.
[b]Δ = differences.
[c]Rats were exposed to anoxia for 25 min (terminated earlier if accelerated grasping occurred) and hyperthermia for 2 hrs at post-natal day 2. Rats were tested at 5, 10, 15, 20, 25, 30 and 45 day of age. Since animals within the same experimental groups did not differ between 5–30 days of life, these data were pooled.
[d]Rats were exposed to anoxia for 25 min (terminated earlier if accelerated grasping occurred) and hyperthermia for 2 hrs at post-natal day 2. Rats were tested at 4 mos of age.
[e]Tested during or immediately after heat stress at 9–10 weeks of age.
[f]Tested at least 4 days after heat stress.
[g]BBB = blood-brain barrier.
[h]Naloxone = 10 mg/kg (i.p.) dose.
[i]Attenuated effects of hyperthermia.

learning and memory. This latter test is sensitive to hippocampal dysfunction [see 42] which may occur in some conditions of heat stress [see 29]. Performance in the open field, forced swim, and water maze tests was not distinguished by early exposure to hyperthermia. However, the hyperthermia-exposed animals spent less time in the center of the open field and less time in the open arms of the plus maze than controls – suggestive of an anxiety-like phenotype. Despite these results, an anxiety-like phenotype would be more convincing if the animals had been evaluated for their responses to anxiolytic drugs, especially since there is some evidence that GABA transmission may be perturbed by hyperthermia (see below). In this experimental design it is unclear whether the reputed anxiety-like behaviors were due to hyperthermia at a young age, possible seizure, or both. Since effects of febrile seizures on cognitive performance in humans are controversial [38, 43, 44], additional tests besides the Morris water maze task are needed to convincingly identify cognitive deficits that may affect spatial and non-spatial cognitive processes, especially if the impairment is mild and is only apparent in certain types of learning and memory tasks.

Besides exerting direct influences on behavioral systems, heat stress can also interact with other physiological conditions to exacerbate its effects. For instance, neonatal asphyxia can lead to a hyperactive phenotype in juvenile rats and hypoactivity in adulthood [45, 46]. Preinatal hypoxia can result in brain damage [47, 48] and exert detrimental effects on cognition and other behaviors [49, 50]. There is some evidence that reductions in body temperature during hypoxia can be neuroprotective [48, 49, 51–54]. To further examine this point, Rogalska and co-workers [45] took two day-old rat pups and exposed them for 25 min to chambers that had been flushed with 100% nitrogen (anoxia) while their rectal temperatures were maintained at 33°C (normal body temperature), 37°C, or 39°C (Table I). These temperatures were maintained for 2 hrs after hypoxia. Since animals at 5–30 days of age did not differ within the neonatal-exposure groups for motor activities, they were collapsed across age into the respective hyperthermia and asphyxia groups. Percent motor activity was augmented with neonatal exposure to hyperthermia and further increased with hypoxia in 5–30 day-old rats; other indices of activity (i.e., distance traveled, linear and angular velocity) were not affected by hyperthermia. However, all activities were increased by neonatal asphyxia and concurrent exposure to 39°C. At 45 days of age, neonatal exposure to 39°C was associated only with increased linear velocity. It should be emphasized that repeated testing of rats in the open field typically leads to habituation and this may have obscured any changes in activity that could have occurred at the given ages. In a separate experiment, telemetry recordings in the home cage failed to discern any effects of neonatal hyperthermia or hypoxia on body temperature or motor activity for any of the ages studied. Hence, results from this study indicate that neonatal exposure to heat stress and asphyxia exert minimal effects on motor responses. Interestingly, other investigators have reported anoxia to have transient effects on motor activity [49, 50, 55].

In a separate investigation, Caputa and colleagues [46] exposed 2-day old neonatal rats to hyperthermia and hypoxia and examined behavioral effects at 4 months of age (Table I). In the plus maze, open arm entries and open arm times were enhanced in adults previously exposed as neonates to increased temperature and hypoxia; neonatal hyperthermia by itself exerted no effects in adulthood. These findings suggest that neither neonatal condition influences the display of anxiety-like responses; however, the high level of illumination (200–350 lux) may have precluded the appearance of this behavior. In the open field, locomotor activities in this novel environment were reduced in adults for animals exposed as neonates to hyperthermia and they were further decreased with neonatal asphyxia at 39°C. Since this 10 min test was run immediately after the plus maze, handling and other effects may have affected the spontaneous activities of the groups. In the familiar environment of the home cage, telemetry was used to monitor activity over 2–4 days. Although motor activities were enhanced only in rats exposed to anoxia at 33°C as neonates, the data were presented as a single bar graph and were not analyzed over the circadian rhythm as in a previous study [see 45]. Interestingly, treatment with deferoxamine (an iron chelator) normalized many of the behavioral deficiencies attributed to combined hyperthermia and apoxia – suggestive that oxidative damage may be contributing to any changes in behavior. In summary, the effects in adulthood of neonatal hyperthermia were not remarkable, whereas effects of hypoxia were more evident.

Effects of heat stress on behavior, neurochemistry, and morphology have been evaluated by Sharma [56] in adult rats exposed to heat stress at 38°C (relative humidity 45–47%) for ½, 1, 2, 3, or 4 hrs (Table I). Rectal temperatures increased linearly over time to 41.5°C. During this time, salivation progressively increased. At the end of 4 hrs of heat exposure, blood pressure declined, PaO_2 was mildly enhanced, $PaCO_2$ was attenuated, and body weight was decreased despite *ad libitum* access to food and water. Locomotor activity was initially increased over the first 2 hrs, but declined by the beginning of the 4th hr due to lethargy and this was further evident as reduced performance on the inclined plane, foot-

print, grid-walking, and rotorod tests. Despite these effects, no changes in righting reflex or thermal nociceptive (tail-flick) responses were observed. Depending upon brain region, levels of glutamate, aspartate, glycine, and GABA increased or decreased over the 4 hr period of heat stress. For example in hippocampus, glycine and GABA were elevated at 2 hrs, but by 4 hrs glycine had returned to normal while GABA was reduced. Glutamate and aspartate were only increased at 4 hrs. These findings suggest that prolonged hyperthermia can promote excitotoxicity that may lead to neural damage. In this regard, 4 hrs of heat stress were sufficient to reduce regional cerebral blood flow, increase permeability of the blood-brain barrier, and produce edema. Microscopy studies indicated that these changes may be due to microvessel collapse, endothelial cell membrane damage and leakage, and perivascular edema. Notably, nerve cell injury with some cell loss was evident in hippocampus. It should be noted that approximately 20% of the animals subjected to heat-stress died and postmortem examination revealed these rats had excessive brain swelling. Since opiate receptor antagonists have been reported to attenuate heat-induced changes in cerebral blood flow, blood-brain barrier permeability, and edema [57], Sharma [56] evaluated effects of naloxone in this heat stress model. Although 1, 5, and 10 mg/kg naloxone were given, only the highest dose was found to reduce salivation, prostration, body temperature, and hypotension, to improve motor responses, prevent changes in neurotransmitters in brain, decrease permeability of blood brain-barrier, and suppress the morphological changes. Despite these beneficial effects, the mechanistic basis of the naloxone responses is unclear since dose-response relationships were not established for any of the neurotransmitter, physiological, or behavioral changes.

Additional experiments have examined neural mechanisms that may be perturbed by heat stress. An electrophysiology study has shown that *in vitro* heating of the hippocampus from 27 to 37°C can increase inhibitory postsynaptic potentials (IPSPs) in CA1 hippocampus [58]. To determine whether increased temperature affects neural inhibition *in vivo*, Liebregts and co-workers [59] used a paired-pulse paradigm to examine responses in the dentate gyrus and CA1 hippocampus. Male 10–17 day-old or adult rats were anesthetized with urethane and the stimulating electrode was placed into the medial perforant pathway with the recording electrode in dentate granule cells. In another experiment the stimulating electrode was positioned in CA3 hippocampus to activate the perforant path with the recording electrode in CA1 hippocampus. A heating pad was used to increase body temperature from normal (37.5°C infant, 36.5°C adult) to 38.8°C (immature and adult rats), or to 40°C (adults only, immature rats didn't survive). No epileptiform activity was observed at any of these temperatures, possibly due to the anticonvulsant activity of urethane [see 60]. In adults hyperthermia at both temperatures increased paired-pulse inhibition in the dentate gyrus and it enhanced excitatory post-synaptic potentials (EPSPs). By comparison, no effects were observed in immature rats at 38.8°C, while in immature rats inhibition in CA1 was reduced. At 40°C paired-pulse inhibition in adult CA1 hippocampus was also decreased. Although there was an increase in EPSPs with temperature across preparations, the effect was only significant for adult dentate gyrus. While the results are subject to alternate interpretations, the most parsimonious explanation may be that hyperthermia promoted seizure in immature hippocampus and this occurred by reducing inhibition on CA1 neurons, whereas in adults decreased CA1 inhibition required higher levels of hyperthermia and seizure susceptibility was altered by the increased inhibition in dentate gyrus. Together, these results indicate that changes in inhibitory neurotransmission, probably through GABA systems, may contribute to seizure under hyperthermic conditions. Despite these findings it must be cautioned that this paired-pulse study only provides indirect evidence that inhibitory transmission may be affected by heat stress.

Currently the mechanisms underlying hyperthermia-induced seizures and accompanying behavioral changes are not clearly defined. However, decreased paired-pulse inhibition in hippocampal CA1 neurons *in vitro* suggests that GABAergic neurotransmission may be affected [59]. To address this question, brain slices from 11–17 day-old rats were prepared and were examined at 32°C (basal), the temperature was increased to 40°C (~2°C/min) and held for 1 min, and then allowed to recover to 32°C (~2°C/min) [61]. Whole-cell recordings were made from CA1 pyramidal cells following stimulation of the CA1 stratum radiatum with an electrode located approximately 0.5 mm from the recording electrode. GABA-A receptor mediated inhibitory post-synaptic currents (IPSCs) were recorded in the presence of *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole proprionic acid (AMPA), and GABA-B receptor antagonists. Heating the slice to 40°C served to decrease the input resistance and the resting membrane potential. The slope of the excitatory post-synaptic current (EPSC) and the maximal inward current were also reduced. With respect to GABA-A receptor responses, increased temperature was observed to decrease the decay time constant and to depress the peak amplitude of GABA-A-mediated IPSCs; the reversal potential was not changed. Upon return to 32°C, the EPSC

slope and maximal inward current immediately returned to baseline. Although the IPSC decay time constant was restored, the IPSC peak amplitude recovered only partially within the first minute with full recovery occurring 5 minutes later. Notably, these effects could not be attributed to hypoxia or to changes in metabolic rate. Since the hyperthermic effects appeared to affect IPSC characteristics more than those underlying the EPSCs and because GABA uptake is enhanced with hyperthermia [62, 63], effects of hyperthermia on IPSCs were evaluated in the presence of the GABA transporter blocker SKF89976A. At 32°C this blocker increased the IPSC decay time constant, while peak amplitude was unaffected. At hyperthermia, the decay time constant was not altered; however, the decline in peak amplitude was attenuated with the drug. Hence, alterations in GABA transport can only partially account for effects of hyperthermia. Collectively, these data were interpreted to indicate that the hyperthermic effects on GABA-A mediated responses are more pronounced than those for excitatory neurotransmission. Due to these influences and because hyperthermia can increase long-term potentiation [59, 64], the balance between excitatory-inhibitory transmission may be shifted to increased excitation; thereby, contributing the generation of febrile seizure.

In a subsequent study, Qu and Leung [65] evaluated whether the hyperthermia-induced effects on GABAergic function could be attributed to pre- or postsynaptic mechanisms, or both. Essentially a paradigm identical to that of Qu and co-workers [61] was employed except spontaneous IPSCs (sIPSCs) and miniature IPSCs (mIPSCs) were recorded. The frequencies of both types of IPSPs were reduced by hyperthermia and, upon return to 32°C, there was some recovery in mIPSP frequencies but they did not return to baseline values. In another experiment, forskolin – which is known to enhance hippocampal pre-synaptic GABA release [66] – prevented the hyperthermia-induced depression of evoked IPSCs and this influence was abrogated by the selective protein kinase A inhibitor H89. Alterations in protein kinase C activity proved ineffective. Further support for this notion occurred when 4-AP (a K^+ channel blocker) normalized the evoked IPSC peak amplitude under hyperthermia. Although these findings support the idea that GABAergic pre-synaptic mechanisms are perturbed by increased temperature, postsynaptic mechanisms also appear to be involved because increased temperature impacted peak amplitudes and the decay time constants of the mIPSCs. Non-stationary noise-analyses suggested that hyperthermia reduced the total number of GABA-A receptors that opened during peak mIPSCs. These latter effects could be mediated through a number of different GABA-specific mechanisms that affect subunit phosphorylation, trafficking, internalization, ligand association/dissociation with the receptor, as well as other mechanisms that affect GABAergic function such as cannabinoids [c.f., 62]. Despite these intriguing electrophysiological findings, they may or may not be relevant to effects of hyperthermia encountered *in vivo* since core temperatures exceeding 40°C can produce substantial neural damage and death [see 23] and because animals and humans encounter heat stress for longer periods of time than the 1 minute imposed in these experiments. Nonetheless, it is possible that GABA dysfunction is one of many sequelae that arise in the course of heat stress.

Effects of hyperthermia on human behavior

One aspect of behavior that has received considerable attention is that of cognitive performance. Although many investigators have reported that heat stress can negatively impact cognition in humans, other researchers have failed to observe any effects or have even noted an improvement in performance [67–78]. Despite these discrepancies, it appears that simple cognitive tasks are resistant to heat stress, whereas more complex tests as well as concurrent tasks may be vulnerable to hyperthermia [79–88]. Factors affecting performance include gender [89], age [see 90], the experience or skill of the test subject [91], duration of exposure to heat stress [69], rate of change in deep body temperature [82, 84, 85, 92–95], use of incentives for testing [96], feedback on performance [97], task type [79, 80, 83], and the way that temperature is measured [98].

Under prolonged exercise, brain temperatures can be augmented at least 0.2°C higher than core body temperatures [99]. Studies of cognition have indicated that performance is unaffected by heat stress unless deep body temperature becomes elevated above normal and the prevailing consensus is that deterioration of cognitive performance is dependent both upon the severity of heat stress and the complexity of the cognitive task [78, 98, 100, 101]. Since cognitive performance can be affected by alterations in mood, stress hormones, monoamines, and motor performance, a number of researchers have investigated heat stress effects on these variables. McMorris and co-workers [88] studied male recreational athletes who had been habituated to the test chamber (baseline) (Table II). After 15 min in the chamber, a blood draw was taken and subjects were immediately subjected to a series of tasks where the order of testing consisted of random movement generation, verbal short-term memory, spatial short-term memory, choice reaction time, and a mood survey. Subsequently, males were tested

Table II. Behavioral effects of hyperthermia in humans.

Subjects	Exposure	Tests	Results	Reference
Males, ~22 mean years of age ($n=8$)	Baseline, temperate, or heat-stress conditions[a]	Core body temperature	↑ heat-stress	[88]
		Random movement generation	↓ heat-stress	
		Verbal short-term memory	No Δ^b	
		Spatial short-term memory	No Δ^b	
		Choice reaction time	No Δ^b	
		Mood survey	Heat stress: ↑ fatigue, ↓ vigor	
Males and females, 20–30 years of age ($n=15$ subjects/group)	Four groups were run[c]	Pain perception	No group differences in baseline pain scores; subsequently, pain ratings were: HS > AS + HS > AS + HS + CT > AS + CT	[102]
		Cognitive task[d]	No group differences	
Males and females, ~26–32 mean years of age ($n=10$)	Baseline (CON), low skin/core (LL), high skin-low core (HL), high skin/core temperature (HH) with neck-head cooling (HC)[e]	Core, skin, and neck temperatures[f]	Core: ↑ HH condition; no Δ^b HC Skin: ↑ HL, ↑ HH; HC ↓ HL and HH Neck: ↑ LL, ↑ HL, ↑ HH; HC ↓ LL, ↓ HL, ↓ HH	[106]
		Morse tapping task	↑ HH	
		Reaction time	No Δ^b with increased skin temperature; ↓ with increased core temperature; HC had no Δ^b	
		Response accuracy	No Δ^b with increased skin temperature; ↓ with increased core temperature; HC had no Δ^b	
		Bond-Lader visual analogue scale	↓ alertness, contentment, calmness; HC normalized responses	

		Self-perception of heat	↓ thermal comfort across all conditions; HC improved comfort in HH	
Males and females, ~31 mean years of age ($n = 16$)	20°C (CON), 50°C (HOT), HOT plus cold packs to head (HHC)[g]	Core (thermometer pill), skin (right gastrocnemius medialis), forehead, and tympanic temperatures	All temperatures ↑ under HOT and HHC conditions;HHC ↓ core, forehead, and tympanic temperatures	[107]
		Match to sample	No Δ[b]	
		Choice reaction time	No Δ[b]	
		Rapid visual information processing	No Δ[b]	
		Spatial span	HOT: ↓ recall of longest sequence	
		Pattern recognition memory	CON: ↓ % correct answers	

[a]For baseline assessment, subjects (wearing shorts and a shirt) were behaviorally tested in an environmental chamber (36°C, 75% relative humidity, and mean radiant temperature of 35.8°C, with a wind speed of 0.6 m/sec) for 30 min 48 hrs prior to heat stress. In the temperate test, the subject (wearing shorts and a shirt) was placed into an environmental chamber (20°C with 40% relative humidity); in the heat stress condition (subject wore a polyvinyl chloride suit) the chamber was 36°C with 75% relative humidity. In both conditions, upon entering the chamber the subject began cycling for 20 min at a workload of 100 W. He rested for 10 min before repeating 20 min of cycling. After this time he rested for 70 min and took the cognitive tests. He then drank 250 ml of 40 mM NaCl solution and drank more of the solution every 20 min for a 2 hr period. After a 15 min rest, he took the behavioral tests again.

[b]Δ = difference.

[c]At training each subject was exposed to thermal stimulation (46°C for 1 min) on the non-dominant thenar eminence. Subjects rated perception of pain. Subjects were randomly assigned to 4 groups: AS + CT - exposed to auditory vowel-like stimulation while performing a cognitive task, HS - exposed only to noxious heat stimulus (46°C/6 min) without the cognitive task, AS + HS - exposed to heat and auditory stimuli without the cognitive task, and AS + HS + CT - exposed to heat and auditory stimuli with the cognitive task.

[d]Auditory stimulation consisted of vowel-like acoustic stimuli that had a constant frequency of 100 Hz in four formants: "the first, third, and fourth were held constant at their respective center frequencies (F1 = 500 Hz, F3 = 3500 Hz, F4 = 4300 Hz), and the second formant (F2) was modulated "in a sinusoidal fashion between 1000 and 2400 Hz." The stimuli were presented for 2 sec at rates of 6, 8, 10, 12, or 14 Hz. The cognitive task required the subject to state whether there was a change in the rate of F2 modulation in the auditory task and whether the direction was decreasing or increasing.

[e]Subjects visited the laboratory three times. In the first visit (48 hrs before test), subjects were familiarized with the tests. On the second and third visits, cognitive performance was assessed under low skin/core temperature, high skin temperature and low core temperature, and at high skin temperature and high core temperature conditions. In one experimental trial, subjects had their head and neck cooled during the cognitive tasks.

[f]Core temperature was by rectal probe; skin temperatures were at midline on forehead, dorsum of the hand, lateral calf, nape of neck, and lower back.

[g]After a familiarization session, subjects (wearing shorts and t-shirt) participated in three experimental trials with 4–7 days recovery between them. In the CON (20°C, 40% humidity, average wet-bulb globe temperature or WBGT 22.8°C), HOT (50°C, 50% humidity, WBGT 43.1°C), or HHC (WBGT 44.9°C) conditions, subjects walked on a treadmill (10–15 min) at 3–5 km/h. They rested for 45 min and then were tested for 2 hrs. The HHC condition was performed under the same environmental conditions as HOT but with three cool packs applied to the head and one to the neck that were changed every 20 min.

under two conditions: temperate (test subject in shorts and shirt in the 20°C chamber at 40% relative humidity) and heat stress (subject wore a polyvinyl chloride suit in the 36°C chamber at 75% relative humidity). Upon entering the chamber, subjects began cycling on a cycle-ergometer for 20 min at a workload of 100 W, were given a 10 min rest, another 20 min cycling session, and a 70 min rest. At the end of this time, the subject left the chamber, 15 min later blood was drawn and the individual was retested on the behavioral tasks. Core body temperature was measured every 10 min. Heat stress increased core body temperature by 1.1°C and impaired performance only on the random movement generation test; performance on other tasks was unaffected. Heat stress also increased feelings of fatigue and decreased vigor. Some changes in plasma levels of cortisol, serotonin, noradrenalin and adrenalin were also noted. Although heart rate was enhanced in response to increased temperature, neck-head cooling did not alter these responses. Other cardiovascular indices showed little change or some alterations (e.g., stroke volume, cardiac output, systolic blood pressure, total peripheral resistance) when body temperature was increased. However, because the data were analyzed by *t*-tests instead of the appropriate and more robust repeated-measures analysis of variance, it is unclear whether any of the variables would reach significance with this analysis – especially since the numbers of subjects (i.e., $n = 8$) were low. Additionally, because subjects did not have free access to water during the test sessions and lost body weight during heat stress, the heat condition was confounded with dehydration.

In a separate experiment University students were exposed to combinations of noxious heat, auditory stimulation, and a cognitive task [102] (Table II). Tonic heat stimulation (HS) of 46°C over 6 min was applied to the thenar area of the non-dominant hand. Auditory stimulation (AS) consisted of vowel-like acoustic stimuli that had a constant frequency of 100 Hz in four formants: ''the first, third, and fourth were held constant at their respective center frequencies'' (F1 = 500 Hz, F3 = 3500 Hz, F4 = 4300 Hz), and the second formant (F2) was modulated ''in a sinusoidal fashion between 1000 and 2400 Hz.'' The stimuli were presented for 2 seconds at 6, 8, 10, 12, or 14 Hz. The cognitive task (CT) required the student to state whether there was a change in the rate of F2 modulation in the auditory task and whether the direction was decreasing or increasing. Subjects were divided into 4 groups and responses to pain sensitivities were compared. One group received noxious HS alone. A second group received the noxious HS and auditory stimulation. A third group encountered auditory stimulation (vowel-like acoustic signals) while performing the cognitive task. A final group was exposed to the noxious HS and auditory stimulation while performing the cognitive task. Subjects rated pain intensity after each test and were evaluated four times. No group differences were found in baseline pain rating scores. Subsequently, the ratings of pain from highest to lowest were: HS > AS + HS > AS + HS + CT > AS + CT. Interestingly, performance on the cognitive tasks was not distinguished by group assignment, possibly because the tasks were not that demanding. Nonetheless, these data indicate that self-reported rating of thermal pain can be influenced by ongoing activities. Despite this finding, it should be emphasized that other investigators have observed considerable variability in patient self-report of pain sensitivity and pain threshold or tolerance [103, 104].

Several researchers have tried to determine whether cooling the brain can affect neuroendocrine, motor, or cognitive function under hyperthermia. Exposure to a sauna at 58°C for 60 minutes was sufficient to elevate skin temperature by ~4°C and core body temperature by ~0.25°C, and to increase prolactin levels in blood by more than 100% [105]. Face-cooling blocked the prolactin-stimulatory effect and was associated with greater thermal comfort by the subjects. In another study male subjects were exposed to a chamber set at 25°C and 50% relative humidity or to a chamber that was increased to 45°C and 50% relative humidity over 30 min [106] (Table II). Effects of manipulating body and skin (forehead, hand, calf, back, nape of neck) temperatures were evaluated according to cardiovascular function, motor function (Morse tapping or button-pressing test), cognition, and self-perception of heat-induced fatigue. The cognitive tasks consisted of simple reaction time, digital vigilance, choice reaction time, and visual processing. Cognitive performance was assessed under three different conditions: low skin and core temperatures at baseline, high skin and low core temperatures immediately after the test chamber temperature had reached 45°C, and at high skin and core temperatures after the body temperature had been increased by 1°C. Subjects were tested without or with neck-head cooling. Neck-head cooling did not affect core body temperature, but did reduce skin temperatures on the forehead and neck. Raising body and skin temperatures reduced feelings of comfort and cooling ameliorated this effect. Similarly, heart rate was decreased by cooling. On the motor test, Morse tapping increased with enhanced temperature while cooling exerted no effects. For the cognitive tasks, reaction-time and accuracy of responding were unaffected by increases in skin heating. However, reaction time and accuracy were reduced with increased core temperature;

cooling was without effect. Results from this experiment suggest that increases in core and skin temperatures may increase feelings of fatigue and lead to some decrements in cognitive performance. Neck-head cooling, however, does not appear to abrogate the mild cognitive deficiency.

Since behavioral tests require a motor response, some investigators have examined effects of heat stress and cooling on cognitive and motor responses [107]. Male and female subjects were randomly tested under three different conditions [control: 20°C with 45% relative humidity, wet bulb globe temperature (WBGT) = 22.8 ± 0.6°C; hot: 50°C with 50% relative humidity, WBGT = 43.1 ± 0.8°C; and hot with head-cooling: WBGT = 44.9 ± 0.8°C) for 2 hrs with a 4–7 day inter-test interval (Table II)]. Subjects were initially familiarized with the cognitive and motor tests. The motor test consisted of electrical stimulation of the tibial nerve while monitoring the compound muscle action potential (M-waves) and reflex waves (H-reflex) during brief (4–5 seconds) and sustained (120 seconds) maximal voluntary contractions of the plantar flexors. Note, the H_{max}/M_{max} ratio was taken as an index of spinal reflex excitability. The cognitive task consisted of matching visual patterns to sample, choice reaction time for two alternative stimuli, pattern recognition memory, visual information processing, and spatial span. At the time of testing, subjects entered the chamber and walked on a treadmill for 10–15 min (3–5 km/hr), rested for 45 min, and then began the cognitive and motor testing. Body, skin (forehead, right gastronemius), and tympanic temperatures were increased under the hot condition, and cooling served to reduce only the forehead and tympanic temperatures but they remained higher than the control. Under the brief voluntary contraction paradigm, torque production was decreased to similar extents by the hot and cooling conditions; voluntary activation was only depressed by the hot condition. This latter effect was accompanied by decreases in neural transmission at the spinal level (H-reflex) and at the neuromuscular junction (M-waves). Under sustained contraction, voluntary activation was further depressed without M-wave failure – suggesting compensation at supraspinal levels. Under hyperthermia, cognitive performance was degraded on the spatial span and pattern recognition memory tasks; cooling only rescued spatial span performance. It should be emphasized that the behavioral responses within groups showed considerable variability. Importantly, although the data were analyzed by repeated-measures analysis of variance tests, comparisons were made separately for control and hot and for control and hot-cooling groups. Since the statistical model should have evaluated the three groups within the same test, the conclusions drawn from this study may not be reliable and they need to be replicated.

In an examination of heat stress effects on motor performance, elbow flexion torque and electromyographic activity of biceps and triceps brachii were measured in male and female subjects (~37 years of age) while core temperature was monitored with an esophageal thermocoupler [108]. Two experiments were conducted. The first was performed in a thermoneutral environment (core temperature = 37.2°C) where responses were measured following electrical stimulation of the brachial plexus or biceps brachii/brachialis motor nerve, or by transcranial magnetic stimulation of the motor cortex following brief or sustained stimulation and following recovery. In the second experiment, subjects consumed warm water and were submerged up to the neck in a water bath to bring core temperatures to 39.5°C. They were removed from the bath, placed into a warm room and tested (core temperature = 38.5°C) as outlined above. During hyperthermia voluntary torque was decreased during brief maximal voluntary contractions, but responses induced by motor cortex stimulation were unaffected. Hence, discharge from cortical motor units may be sufficient to maintain voluntary muscle activation responses to brief stimulation under hyperthermic conditions. Under sustained muscle stimulation, voluntary contractions were further reduced by hyperthermia; responses to cortical activation were enhanced. Thus, with hyperthermia and sustained stimulation there appears to be some reduction in cortical unit activity or cortical fatigue, such that peripheral motor responses decline. These data suggest that both peripheral and central mechanisms can be affected by increased temperature, especially when sustained motor activity is required.

Dewhurst and colleagues [109] have studied effects of heating and cooling in young (mean: 22 years of age) and older (mean 73 years of age) females where muscle (vastus lateralis and soleus) temperatures were increased or decreased by 3°C over baseline. Electromyographic activities of the soleus and tibialis anterior muscles were also monitored. Soleus H-reflexes and M-waves were evoked by electrical stimulation of the posterior tibial nerve. Although alterations in skin (vastus lateralis, popliteal fossa, and soleus) temperatures were observed, tympanic temperatures were unchanged. Electromyographic activities at baseline and under various temperature conditions were similar in both age groups, but the H-reflex output was lower in older females under control and cooling conditions. Cooling increased and warming decreased the latency of the H-reflex. Under these circumstances, localized warming did not affect spinal reflex excitability at either age; however, cooling enhanced the

H-reflex output in younger but not older women. Although body mass for older females was somewhat higher than that for younger females, no body fat or muscle mass index was taken. Possible differences in these indices could have contributed to the some of the age effects on motor performance.

In conclusion these results show that heat stress can affect motor and cognitive performance. Since motor output is required for responses on cognitive tests, some cognitive deficiencies may be attributed to decreased motor performance – especially for tasks that require more complex motor responses (i.e., Morse tapping, etc.). Although it appears that hyperthermia may exert more deleterious effects on complex rather than simple cognitive tasks, there needs to be a more systematic study of the effects of the duration of different levels of hyperthermia on performance across a battery of cognitive tests. Additionally, body temperatures need to be carefully monitored during these tests.

Overview of effects of radiofrequency radiation on behavior

Exposure to radiofrequency radiations (3 kHz to 300 GHz) can produce an internal electric field and related current density within the organism. Although 1 MHz is often sufficient to stimulate excitable tissues in humans, thermal effects on tissues require higher frequencies of stimulation [110]. It should be noted that lethality in rats often results when core body temperatures rise above 42°C; however, death can also ensue when skin temperatures are increased rapidly despite relatively normal core temperatures (~40°C) [see 111]. Biological effects of radiofrequency radiations depend upon orientation to the source of the radiation, wavelength of the radiation, and body size and shape [111, 112]. Generally, the larger the organism, the lower the resonant frequency and the lower the whole body specific absorption rate (SAR) for a certain power density. Hence, higher power densities are required to affect body temperatures. Behavioral responses to continuous and pulsed wave fields appear to be similar as some types of responses are disrupted ~4 W/kg [111]. Despite this fact, it should be noted that 5 W/kg can produce hyperthermia in rat brain, whereas 10 W/kg is required to disrupt performance on the novel object test [113, 114]. Investigators have typically used work stoppage in operant conditioning as an index for the power density threshold for radiofrequency radiation [115–121]. Within this paradigm an increase of ~1°C in whole body temperature will disrupt ongoing responses if the animals are oriented continually towards the source of the radiation. Since this point is controversial, it has been suggested that there may be local ''hotspots'' and that local SAR, rather than whole body SAR may be the more sensitive index of radiofrequency radiation exposure [118, 122]. Nevertheless, it should cautioned that work stoppage in animal studies may not indicate adverse effects of the exposure, but may reflect instead habituation or attempts to cool-off, escape, or engage in other responses [123]. Importantly, the specific brain locus or mechanism (e.g., autonomic or biochemical changes) mediating the work stoppage response has yet to be defined.

Effects of radiofrequency radiation on behavior

Effects of electromagnetic field radiation on cognitive performance have been investigated in animals and humans. Past research has shown that in both cases, radiation can facilitate, impair, or produce no effects on performance [see 111, 124]. Usually, effects of radiation are measured in terms of changes in response rate or reaction time. In animals, facilitation in performance has been observed at 13 W/kg, whereas deficiencies are noted at less than 4 W/kg. Although it is clear that radiofrequency radiation can interfere with operant behaviors, effects on cognitive performance are less convincing. Yamaguchi and colleagues [125] exposed adult male rats to a 1439 WmHz pulsed time-division multiple-access field (50 Hz, 1/3 duty ratio, 6.7 millisecond pulse-width) (Table III). Animals were subjected to two different exposure protocols. In one, rats were given acquisition training for 4 days in a T-maze, had a 4 day hiatus, and were divided into four groups. These groups consisted of home-cage housed, sham-exposed, or rats given a brain average SAR of 7.5 W/kg (peak SAR = 11 W/kg; whole body average SAR = 1.7 W/kg, peak SAR = 32 W/kg) for 1 hr/day or 25 W/kg (peak SAR = 39 W/kg; whole body average SAR = 5.7 W/kg, peak SAR = 110 W/kg) for 45 minutes. Both groups were exposed to electromagnetic field radiation for 4 days while receiving reversal T-maze training after each exposure. Note, the 45 minute exposure was used for the 25 W/kg group because 60 minute exposures were stressful to the rats and they were unable to perform the task. Under the second protocol, rats were run as in the first, except they were divided into three groups: home-cage housed, sham-exposed, or were given a brain average SAR of 7.5 W/kg (peak 11 W/kg) for 1 hr/day for 5 consecutive days, followed by a 2-day rest-period, over three cycles. Animals were tested for T-maze reversal in the final 5-day block of microwave exposure. Intraperitoneal temperatures were monitored during the time of microwave exposure and temperatures were only increased by 2°C in the 25 W/kg group. Only the 25 W/kg

Table III. Effects of radiofrequency radiation on behavior in rodents.

Animals	Exposure	Tests	Results	Reference
Male Sprague-Dawley rats (675 ± 70 g); $n = 15$–24 rats/group	1439 mHz pulsed time-division multiple-access field (50 Hz, 1/3 duty ratio, 6.7 msec pulse width)[a]	Intraperitoneal temperature	↑ 2°C in the 25 W/kg group	[125]
		T-maze	↓ performance 25 W/kg group	
Male Sprague-Dawley rats (250–300 g); $n = 8$ rats/group	2 μs pulses, 500 pulses/second at 2450 mHz[b]	Radial arm maze	Performance of sham similar to radiated rats	[126]
Male albino Kunming mice; $n = 10$ mice/group	Average power densities of 5, 10, 25, or 50 mW/cm^2 for 20 min prior to each test	Rectal temperature	Temperature ↑ 0.7 and 2.3°C with 25 and 50 mW/cm^2 exposures	[127]
		Multiple-trial passive avoidance	↑ number of acquisition trials and ↓ latency to cross with 50 mW/cm^2	
		Cell numbers in CA2 hippocampus	↓ with 50 mW/cm^2	
		Cell numbers in amygdala	No Δ[c]	
Male Wistar rats (21 days of age); $N = 6$ rats/group morphology, $n = 18$ rats/group behavior	900 mHz, 0.577 msec pulse duration, 217 Hz pulse frequency for 2 hrs/day 5 days/week for 5 Weeks[d]	Open field activity	No Δ[c]	[128]
		Elevated plus maze	No Δ[c]	
		Startle response	No Δ[c]	
		Prepulse inhibition	No Δ[c]	
		Morris water maze	↑ performance in radiation-exposed rats	
		Gross brain histology	No Δ[c]	
		Apoptosis in dentate gyrus	No Δ[c]	
		Doublecortin + area of granule cells	No Δ[c]	
		pCREB + granule cells	No Δ[c]	
		Blood-brain barrier permeability	No Δ[c]	

[a]There were two different exposure protocols. In one, rats were given acquisition training for 4 days in a T-maze, had a 4 day hiatus, and were divided into four groups: home-cage housed, sham-exposed, given a brain average SAR of 7.5 W/kg (peak SAR = 11 W/kg; whole body average SAR = 1.7 W/kg, peak SAR = 32 W/kg) for 1 hr/day, or given 25 W/kg (peak SAR = 39 W/kg; whole body average SAR = 5.7 W/kg, peak SAR = 110 W/kg) for 45 minutes. Radiation exposure was for 4 days while undergoing reversal T-maze training after each exposure. Under the second protocol, rats were run as in the first, except they were divided into three groups: home-cage housed, sham-exposed, or given a brain average SAR of 7.5 W/kg (peak 11 W/kg) for 1 hr/day for 5 consecutive days, followed by a 2-day rest-period, over three cycles.
[b]The radiation delivered a whole body SAR of 0.6 W/kg for 45 min and then were tested immediately in the maze.
[c]Δ = difference.
[d]Animals were assigned to 3 different groups: sham control, a low-dose group (whole body averaged SAR of 0.3 W/kg), and a high-dose group (whole body SAR of 3 W/kg). Animals behaviorally tested or morphologically evaluated at the end of radiation exposure.

group showed some impairment in reversal T-maze performance. Although these findings confirm that increases in body temperature by more than 1°C are sufficient to disrupt behavior, it is unclear whether the mechanism underlying the disturbance is due to biological (e.g., effects on neural transmission, signal transduction, etc.) or psychological processes (e.g., response competition, etc.). Additional problems relate to the fact that 75–86% of the rats failed to acquire the task. Although no group differences were observed prior to reversal testing, animals were not trained to a criterion before microwave exposure so their variability in response may have obscured any possible effects of the 7.5 W/kg treatments. Moreover, there was only a single index of performance in the T-maze, ''mean correct choices,'' and this was examined daily over two blocks of 8 trials each. This single index of response was sufficient to discriminate gross differences between the 25 W/kg and control group, but it might not have been sensitive to subtle changes in behavior that occurred within the 7.5 W/kg group. For this reason, additional indices of behavior should have been taken, such as latency to reach the reinforced arm, latency to reach the goal cup, speed of locomotion in the maze, latency to eat, and numbers of perseverative errors. Responses on individual trials should have been analyzed and presented. Finally, since the average body weights of the rats at the beginning of the experiment were 675 ± 70 g, age and weight of the animals may have reduced the probability of detecting effects of the 7.5 W/kg treatments.

Effects of electromagnetic field radiation on working memory have also been evaluated in the 12-arm radial maze [126] (Table III). Adult male rats were exposed for 45 min over 10 days to pulsed electromagnetic field radiation (2 μs pulses, 500 pulses/second at 2450 mHz) delivering an average whole body SAR of 0.6 W/kg and tested in the maze immediately after each exposure. Performance in the maze was not different between the sham or radiation-exposed groups. Hence, under these conditions electromagnetic field radiation exposure did not influence working memory processes in rats. Unfortunately, effects of radiation on body temperatures were not reported.

Besides appetitive paradigms, effects of electromagnetic field radiation have been examined on aversive behaviors. Male mice were subjected to sham or radiation exposures at power densities of 5, 10, 25, or 50 mW/cm^2 [127] (Table III). At some time following a 20 min exposure, animals were tested in a multiple-trial inhibitory avoidance paradigm where they were repeatedly conditioned in a passive avoidance chamber until they remained on the lighted side for 60 seconds; retention testing occurred 24 hrs later. After this latter time, mice were euthanized and brains were taken for hemotoxylin and eosin staining for cell counting in hippocampus and amygdala. After radiation exposure, rectal temperatures were increased by ~0.7 and 2.3°C for the 25 and 50 mW/cm^2 groups, respectively. The numbers of acquisition trials increased, while the latency to cross to the darkened chamber at 24 hrs was decreased in the 50 mW/cm^2 group compared to the sham controls. Cell numbers in CA2 hippocampus were also reduced in the 50 mW/cm^2-exposed group; no differences in amygdala cell numbers were noted. Interestingly, when 25 mg/kg theophylline (i.p.) was given 30 min before radiation exposure, acquisition of the task was normalized in 50 mW/cm^2-exposed group; retention was still deficient and the numbers of hippocampal cells were not examined. This study re-affirms that increases in body temperature greater than 1°C disrupt cognitive performance. Although there was a tendency for the 25 mW/cm^2-exposed group to display some deficiencies, the effects were not significant. Since hippocampal cell number was affected only in the 50 mW/cm^2-exposed group, additional more selective tests for hippocampal dysfunction, such as contextual fear conditioning, object recognition memory, and social transmission of food preference where both short- and long-term memory processes are examined, should have been used – especially with regards to the 25 mW/cm^2 group.

Additional investigators have also analyzed effects of electromagnetic field radiation on brain morphology and behavior. Male rats beginning at 24 days to 8 weeks of age were exposed to radiofrequency radiation (900 MHz, pulse duration of 0.577 milliseconds, pulse frequency of 217 Hz) for 2 hrs/day for 5 days/week [128] (Table III). Animals were assigned to three different groups: sham control, a low-dose group (whole body averaged SAR of 0.3 W/kg), and a high-dose group (whole body SAR of 3 W/kg). At the end of the experiment, rats were submitted to histology/immunohistochemistry or behavioral testing (spontaneous activity for 5 min in the open field, plus maze, startle response and prepulse inhibition, and Morris water maze). No differences in body weights were observed among the groups following radiation exposure. Additionally, no group differences were noted on any of the behavioral tests, except the Morris water maze where radiation-exposed rats learned the location of the hidden platform more quickly than controls. Morphology studies failed to detect any group differences with regards to dying neurons, degenerative changes, or leakage of the blood-brain barrier. Although no measure of possible thermal effects was presented, these data suggest that this level and

duration of radiofrequency exposure is not deleterious to behavior.

Besides animal experimentation, a number of investigators have also recently examined effects of mobile phone emissions on brain function in humans [c.f., 129–134]. Some researchers have found that electromagnetic field radiation facilitates memory processes, while others observe no effect. None of the studies has been replicated. In an attempt to replicate an earlier study [135], Krause and co-workers [136] mounted a digital phone over an adult male subject's left posterior temporal lobe while they performed an auditory memory test. The phone emitted 902 MHz at a frequency of 217 Hz with a pulse-width of 0.577 milliseconds at a power of 0.25 W. The SAR values were 0.878 and 0.648 mW/g averaged over 1 and 10 g of tissue. Electroencephalograms were taken while the phone was ''on'' or ''off''; the total test time for this within subject experiment was ~60 minutes. Although higher numbers of errors occurred when the phone was ''on'' than ''off'' and early (100–500 milliseconds) and event-related synchronizations in the 4–6 and 6–8 Hz bands were decreased, these behavioral results did not replicate their earlier study [135]. Moreover, in the previous report they observed changes in all frequencies of electroencephalographic activity examined, not just in the first two bands.

In another attempt to replicate earlier work where electromagnetic field radiation facilitated cognitive performance [131], Haarala and colleagues [137] used the same phones as described above while subjecting males and females to different cognitive tasks. Notably, the subjects were tested in two independent laboratories, one in Finland and the other in Sweden. The replicate tests consisted of a simple reaction time task, a two-choice reaction-time, a ten-choice reaction-time, a subtraction, a verification, a vigilance, and three additional tasks composed of modified Stroop tests. The same subjects were tested with the phone ''on'' or ''off'' with sessions separated by 24 hrs. Unfortunately, this experimental design was confounded because reaction times for subjects were shorter on the same tasks on test day 2. No effects of radiation exposure were observed. Hence, these results fail to replicate those from Koivisto and co-workers [131].

In a separate study, these same investigators [138] examined effects of electromagnetic field radiation on short-term memory processes using the subjects and phones described above [137]. The average SAR was slightly higher (0.683 versus 0.990 W/kg) in the present study. The skin temperature at the location of phone-contact was increased by 1.5°C and maintained after 20–40 minutes when the phone was ''on.'' Subjects were tested twice, under sham (phone ''off'') or radiation (phone ''on'') conditions, separated by 24 hrs. As in the previous experiment [137], a learning effect was evident where reaction times were shorter on test day 2 than day 1 regardless of memory load. Overall, electromagnetic radiation did not affect short-term memory processes in this experiment.

Other researchers have exposed different sides of the head to radiofrequency radiation while performing cognitive tasks that reputedly rely more upon one cerebral hemisphere than another [139]. Adult male right-handed subjects were evaluated on a verbal item recognition task, a spatial item recognition task, and two different spatial compatibility tests. Subjects were tested over 2 hrs with a 5 minute inter-test interval. They were exposed alternately on the left or right side or sham-exposed to 890.2 MHz with a pulse width of 0.577 milliseconds at a power of 0.25 W. Responses were faster in the second session than the first signifying a training effect. Reaction times on the verbal and spatial recognition and the spatial compatibility tests were faster with the right than left hand, confirming the subjects were right-handed. There was also some evidence that radiation exposure slowed only left-hand responding in these same tests. These results are difficult to interpret because it is unclear why microwave exposure, irrespective of task, would only affect responses with the left hand unless handedness or some additional variable was confounded.

In a study by the same group, male right-handed subjects were subjected to only one of three conditions: sham, left-side, or right-side of head exposure [140]. The same characteristics of radiofrequency radiation were used with SARs ranging from 0.54 to 1.09 W/kg, depending upon phone position. Subjects were evaluated on a spatial working memory task over two test sessions. Again, a training effect was evident since performance on the second session was superior to the first, and right-hand were faster than left-hand responses. As in the previous study, the results are difficult to interpret. Some clarity may have been rendered if the one-half of the subjects had used the right hand for matches and the left for mismatches, while the remaining half were trained to respond in an opposite fashion.

Some subjects who use mobile phones have reported incidences of headache, dizziness, or other types of discomfort or pain [141]. These symptomatic subjects were compared to non-symptomatic males and females in a virtual Morris water maze during left-head exposure to 884 MHz set to non-discontinuous or discontinuous transmission modes with psSAR10 g of 1.95 and 0.23 W/kg, respectively. Performance improved in the symptomatic group with radiation exposure, whereas no effects were observed in the non-symptomatic group. However, since the symptomatic group contained more women

than men, it may be the case that performance of females is more sensitive to microwave radiation than men. These results need to be replicated and extended using more conventional tests of cognition.

Besides electromagnetic field exposure from mobile phones, some investigators have examined effects of living in proximity to a mobile phone base station. In a large study, 365 subjects were assigned to three groups according to estimates of maximal power density: ≤ 0.1, 0.1 to 0.5, and $>0.5\,mW/m^2$ [142]. Subjects had to be exposed the high frequency electromagnetic fields for at least 8 hrs a day for 1 year. They were evaluated according to subjective symptoms, memory processes, reaction time, and perceptual speed. Only perceptual speed and some subjective symptoms (i.e., headaches, cold hands or feet, difficulty in concentrating) were enhanced with increased exposure levels. It should be emphasized that when subjects who reported head pain and discomfort with cell phones were evaluated in a double blind experiment, no evidence was obtained supporting these subjective symptoms [143]. Collectively, these findings suggest that very few behavioral abnormalities, if any, result from exposure to low power densities of high frequency electromagnetic fields.

By comparison, in a cross-sectional study of 165 subjects Abdel-Rassoul and colleagues [144] reported that proximity to a mobile phone base station for 8–15 hrs a day was associated with some behavioral dysfunction. Subjects were queried for neuropsychiatric complaints and evaluated on a variety of neurobehavioral tests. Subjects that lived under the antenna or in a building opposite the antenna expressed more complaints and performed less satisfactorily on a test of auditory attention and short-term memory than subjects living at least 2 kilometers from the base station. However, these former subjects performed superior to controls on tests of visuomotor performance and attention. Subjects living opposite the antenna had lower performance scores on problem solving than those living in the building under the antenna. These data, as for all other electromagnetic field radiation experiments, need to be replicated and, in some cases, other factors (socioeconomic status) need to be controlled.

In summary, it appears that electromagnetic field radiation emitted at levels comparable to mobile phone use produces conflicting effects on behavior where cognition is facilitated, impaired, or not changed. Most of the experiments to date suffer from irreproducibility even by the original investigators. This suggests either that the radiation level is at a threshold where some individuals are affected while others are not, or that the level is innocuous. There is evidence, however, that some individuals may be more susceptible to experiencing certain neuropsychological effects (e.g., sleep disturbance, headache, etc.) than others. Nonetheless, thermal changes appear to account for almost all of the behavioral effects reported.

A theoretical model of heat-stress effects on cognitive performance

A limitation in interpreting effects of heat stress on cognitive responses has been the lack of a firm theoretical framework on which to design experiments and to interpret results. Traditionally, classical arousal theory has been used for this purpose. This theory predicts that arousal and performance can be described as an inverted U-shaped function [145–147]. As applied to heat stress, increases in environmental temperatures produce a concomitant enhancement in arousal and an improvement in cognitive performance. However, at some point performance reaches a maximum and further increases in temperature lead to decrements in performance. In practice, this theory is descriptive, not quantitative, its predictive power is limited, and arousal may be multimodal [148–150]. Moreover, the inverted U-shaped function has been rarely quantified by investigators [148,150,151]. In an attempt to better describe effects of heat stress, the Maximal Adaptability Model has been proposed [152]. This theory was originally developed to describe changes in behavioral performance due to heat stress as reflecting alterations in attentional resources. Under low heat stress conditions (i.e., hypostress), performance is not impeded. As the levels of stress increase, the zone of maximal adaptability is reached and adjustments to the attentional demands of the task are easily achieved such that performance remains the same or may even increase. After this point, increased intensities of stress lead to decrements in performance.

Although the Maximal Adaptability Model was originally adopted to explain heat stress effects on attention, it has now been expanded to include cognitive performance. To test this idea, Vasamatzidis and colleagues [97] took 12 male students (22–30 years of age) and exposed them to six different climates of 22, 28, and 34°C (wet bulb globe temperatures or WBGT) in combination with 30 and 70% relative humidity while they were engaged various behavioral tests. These tasks included display monitoring (DS), math processing (MP), memory search (MS), unstable tracking (UT), and the composite score from SYNTASK. The latter test as composed of 4 simultaneous tasks consisting of the Sternberg memory search task, an arithmetic task, visual monitoring, and an auditory

discrimination. Subjects were exposed to only one climate on any given day with a rest day interposed between test days. The daily 2 hr test was divided into four 30-minute periods. Tests were presented for a each period in the following invariant order: DM with MP, MS with MP, UT with MS, SYNTASK, DM with MP, MS with MP, and UT with MS. Heart rate and ear temperature were monitored during the tests.

Prior to testing, subjects received 7 training trials. At the end of training, performance was very stable. The results indicated that working memory (i.e., MS and MP) were resistant to heat stress effects, whereas manual responses (i.e., UT) were most susceptible to stress. Under time-sharing conditions (i.e., DM, SYNTASK-visual monitoring and SYNTASK-auditory discrimination), heat stress negatively impacted performance. Surprisingly, humidity was often inconsequential; however, interactions between temperature and humidity were apparent as performance at 22°C and 30% relative humidity was superior on the MS and UT tasks relative to those at 34°C and 70% relative humidity. In summary, results from this experiment imply that only manual responses are impacted with heat stress. It should be emphasized that the reliability of these findings will depend upon their ability to be replicated by other investigators. Furthermore, since the study was run with college students, it is unclear to what extent these laboratory data can be generalized to other groups. Moreover, the cognitive tasks that were employed may not have been demanding enough to rigorously and systematically assess cognitive performance. For the most part since cognitive performance was not affected by heat stress, it is unclear the extent to which the Maximal Adaptability Model can be applied to evaluating effects of heart stress on resource allocation in cognitive function, especially because resource allocation may vary in different ways according to the requirements and specificity of the behavioral task. Although this model has heuristic value, it presumes that various pre-existing subject conditions (e.g., prior experience, anxiety, depression), environmental factors (e.g., humidity, time of day), task demands, and cognitive abilities are homogeneous and impinge upon cognitive processes in similar manners.

Acknowledgements

The contents of this review were supported by Microwave Manufacturers Foundation and the GSM Association.

Declaration of interest: I wish to declare that I have no conflicts of interests in this work.

References

1. O'Callaghan JP, Holtzman SG. Quantification of the analgesic activity of narcotic antagonists by a modified hot-plate procedure. J Pharm Exp Ther 1985;192:497–505.
2. Bannon AW, Gunther KL, Decker MW. Is epibatidine really analgesic? Dissociation of the locomotor activity, temperature, and analgesic effects of (±)-epibatidine. Pharmacol Biochem Behav 1995;51:693–698.
3. King TE, Joynes RW, Payne M. The tail-flick test: II. The role of supraspinal systems and avoidance learning. Behav Neurosci 1997;111:754–767.
4. Moskowitz AS, Terman GW, Liebeskind JC. Stress-induced analgesia in the mouse: Strain comparisons. Pain 1985;23:67–72.
5. Rubinstein M, Mogil JS, Japon M, Chan EC, Allen RG, Low MJ. Absence of opioid-stress-induce analgesia in mice lacking β-endorphin by site-directed mutagenesis. Proc Natl Acad Sci USA 1996;93:3995–4000.
6. Mogil JS, Belknap JK. Sex and genotype determine the selective activation of neurochemically-distinct mechanisms of swim stress-induced analgesia. Pharmacol Biochem Behav 1997;56:61–66.
7. Crawley JN. What's wrong with my mouse? Behavioral phenotyping of transgenic and knockout mice. New York: Wiley-Liss: 2000, pp 65–81.
8. Saeki S, Yaksh TI. Suppression of nociceptive responses by spinal mu opioid agonists: Effects of stimulus intensity and agonist efficacy. Anesth Analges 1993;77:265–277.
9. Chakour MC, Gibson SJ, Bradbeer M, Helma RD. The effect of age on Aδ- and C-fiber thermal pain perception. Pain 1996;64:143–152.
10. Yeomans DC, Pirec V, Proudfit HK. Nociceptive responses to high and low rates of noxious cutaneous heating are mediated by different nociceptors in the rat: Behavioral evidence. Pain 1996;68:133–140.
11. McCormack K, Prather P, Chapleo C. Some new insights into the effects of opioids in phasic and tonic nociceptive tests. Pain 1998;78:79–98.
12. Bodnar RJ, Romero M-T, Kramer E. Organismic variables and pain inhibition: Roles of gender and aging. Brain Res Bull 1988;21:947–953.
13. Hamm RJ, Knisely JS. Developmental aspects of nociception. Brain Res Bull 1988;21:933–946.
14. Vierck CJ, Acosta-Rua AJ, Rossi HL, Neubert JK. Sex differences in thermal pain sensitivity and sympathetic reactivity for two strains of rat. J Pain 2008;9:739–749.
15. Riley J III, Robinson M, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: A meta-analysis. Pain 1998;74:181–187.
16. Watson PJ, Latif RK, Rowbotham DJ. Ethnic differences in thermal pain responses: A comparison of South Asian and White British healthy males. Pain 2005;118:194–200.
17. Berge O-G, Garcia-Cabrera I, Hole K. Response latencies in the tail-flick test depend upon tail skin temperature. Neurosci Lett 1988;86:284–288.
18. Hole K, Berge O-G, Tjolsen A, Eide PK, Garcia-Cabrera I, Lund A, Rosland JH. The tail-flick test needs to be improved. Pain 1990;43:391–392.
19. Dirig DM, Salami A, Rathbun ML, Ozaki GT, Yaksh TL. Characterization of variable defining hindpaw withdrawal latency evoked by radiant thermal stimuli. J Neurosci Methods 1997;76:183–191.
20. Lee JH, Stitzer ML. A novel radiant heat test for assessing pain threshold in human subjects: Measurement stability. Behav Res Meth Instrument Comput 1995;27:41–45.
21. Greenwald MK, Johanson C-E. Behavioral measurement of thermal pain sensitivity in humans: Effects of stimulus

intensity and instructions. Exper Clin Psychopharm 2001;9:209–214.
22. Wasner GL, Brock JA. Determinant of thermal pain thresholds in normal subjects. Clin Neurophysiol 2008;119:2389–2395.
23. Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002;346:1978–1988.
24. National Institute for Occupational Safety and Health. Criteria for a recommended standard – Occupational exposure to hot environments. Washington, D.C.: U.S. Government Printing Office, NIOSH: 1986, No. 72–10269.
25. van den Berg BJ, Yerushalmy J. Studies on convulsive disorders in young children. Pediatr Res 1969;3:298–304.
26. Nelson KB, Ellenburg JH. Prognosis in children with febrile seizures. Pediatrics 1978;61:720–727.
27. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia 1994;35:S1–S6.
28. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol 2002;17:S44–S52.
29. van Landingham KE, Heinz ER, Cavazos JE, Lewis DV. Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. Ann Neurol 1998;43:413–426.
30. Rocca WA, Sharbrough FW, Hauser WA, Annegers JF, Schoenberg BS. Risk factors for complex partial seizures: A population-based case-control study. Ann Neurol 1987;21:22–31.
31. Maher J, McLachlan RS. Febrile convulsions. Is seizure duration the most important predictor of temporal lobe epilepsy? Brain 1995;118:1521–1528.
32. Chen K, Baram TZ, Soltesz I. Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. Nat Med 1999;5:888–894.
33. Chen K, Aradi I, Thon N, Eghbal-Ahmadi M, Baram TZ, Soltesz I. Persistent modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. Nat Med 2001;7:331–337.
34. Holtzman D, Oban K, Olson J. Hyperthermia-induced seizures in the rat pup: A model for febrile convulsions in children. Science 1981;213:1034–1036.
35. McCaughran Jr JA, Schechter N. Experimental febrile convulsions: Long-term effects of hyperthermia-induced convulsions in the developing rat. Epilepsia 1982;23:173–183.
36. Baram TZ, Gerth A, Schultz L. Febrile seizures: An appropriate aged model suitable for long-term studies. Dev Brain Res 1997;98:265–270.
37. Dube C, Chen K, Eghbal-Ahmadi M, Brunson K, Soltesz I, Baram TZ. Prolonged febrile seizures in the immature rat model enhance hippocampal excitability long term. Ann Neurol 2000;47:336–344.
38. Kornelsen RA, Boon F, Leung. LS, Cain DP. The effects of a single neonatally induced convulsion on spatial navigation, locomotor activity and convulsion susceptibility in the adult rat. Brain Res 1996;706:155–159.
39. Shibasaki K, Suzukim M, Mizuno A, Tominaga M. Effects of body temperature on neural activity in the hippocampus: Regulation of resting membrane potentials by transient receptor potential vanilloid 4. J Neurosci 2007;27:1566–1575.
40. Gibson HE, Edwards JG, Page RS, Van Hook MJ, Kauer JA. TRPV1channels mediate long-term depression at synapses on hippocampal interneurons. Neuron 2008;57:746–759.
41. Mesquita AR, Tavares HB, Silva R, Sousa N. Febrile convulsions in developing rats induce a hyperanxious phenotype later in life. Epilepsy Behav 2006;9:401–406.
42. Morris RGM, Garrud P, Rawlins JNP, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. Nature 1982;297:681–683.
43. Werboff J, Havlena J. Febrile convulsions in infant rats, and later behavior. Science 1963;142:684–685.
44. Nealis JG, Rosman NP, De Piero TJ, Ouellette EM. Neurologic sequelae of experimental febrile convulsions. Neurology 1978;28:246–250.
45. Rogalska J, Caputa M, Wentowska K, Nowakowska A. Stress-induced behaviour in juvenile rats: Effects of neonatal asphyxia, body temperature and chelation of iron. Behav Brain Res 2004;154:321–329.
46. Caputa M, Rogalska J, Wentowska K, Nowakowska A. Perinatal asphyxia, hyperthermia and hyperferremia as factors inducing behavioural disturbances in adulthood: A rat model. Behav Brain Res 2005;163:246–256.
47. Ginsberg MD. Temperature influences on ischemic brain injury. In: C.Y. Hsu (ed.), Ischemic stroke: From basic mechanisms to new drug development. Monogr Clin Neurosci 1998; 16: 65–88.
48. Reglodi D, Somogyvari-Vigh A, Maderdrut JL, Vigh S, Arimura A. Postischemic spontaneous hyperthermia and its effects in middle cerebral artery occlusion in the rat. Exp Neurol 2000;163:399–407.
49. Dell'Anna ME, Calzolari S, Molinari M, Iuvome L, Calimici R. Neonatal anoxia induces transitory hyperactivity, permanent spatial memory deficits and CA1 cell density reduction in developing rats. Behav Brain Res 1991;45:125–134.
50. Nyakas C, Buwalda B, Luiten PGM. Hypoxia and brain development. Prog Neurobiol 1996;49:1–51.
51. Yager J, Towfighi J, Vannucci RC. Influence of mild hypothermia on hypoxic-ischemic brain damage in the immature rat. Pediatr Res 1993;34:525–529.
52. Colbourne F, Sutherland G, Corbett D. Postischemic hypothermia. A critical appraisal with implications for clinical treatment. Mol Neurobiol 1997;14:171–201.
53. Corbett D, Hamilton M, Colbourne F. Persistent neuroprotection with prolonged postischemic hypothermia in adult rats subjected to transient middle cerebral artery occlusion. Exp Neurol 2000;163:200–206.
54. Maier CM, Sun GH, Kunis D, Yenari MA, Steinberg GK. Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: Neurological outcome and infarct size. J Neurosurg 2001;94:90–96.
55. Speiser Z, Korczyn AD, Teplitzky I, Gitter S. Hyperactivity in rats following postnatal anoxia. Behav Brain Res 1983;7:379–382.
56. Sharma HS. Hyperthermia influences excitatory and inhibitory amino acid neurotransmitters in the central nervous system. An experimental study in the rat using behavioural, biochemical, pharmacological, and morphological approaches. J Neural Trans 2006;113:497–519.
57. Sharma HS, Westman J, Cervos-Navarro J, Dey PK, Nyberg F. Opioid receptor antagonists attenuate heat stress-induced reduction in cerebral blood flow, increased blood-brain barrier permeability, vasogenic edema and cell changes in the rat. Ann NY Acad Sci 1997;813:559–571.
58. Thompson SM, Masukawa LM, Prince DA. Temperature dependence of intrinsic membrane properties and synaptic potentials in hippocampal CA1 neurons *in vitro*. J Neurosci 1985;5:817–824.
59. Liebregts MT, McLachlan RS, Leung LS. Hyperthermia induces age-dependent changes in rat hippocampal excitability. Ann Neurol 2002;52:318–326.
60. Cain DP, Raithby A, Corcoran ME. Urethane anesthesia blocks the development and expression of kindled seizures. Life Sci 1989;44:1201–1206.
61. Qu L, Liu X, Wu C, Leung LS. Hyperthermia decreases GABAergic synaptic transmission in hippocampal neurons of immature rats. Neurobiol Disease 2007;27:320–327.

62. Al-Hayani A, Davies SN. Effect of cannabinoids on synaptic transmission in the rat hippocampal slice is temperature-dependent. Eur J Pharmacol 2002;442:47–54.
63. Binda F, Bossi E, Giovannardi S, Forlani G, Peres A. Temperature effects on the presteady-state and transport-associated currents of GABA cotransporter rGAT1. FEBS Lett 2002;512:303–307.
64. Masino SA, Dunwiddie TV. Temperature-dependent modulation of excitatory transmission in hippocampal slices is mediated by extracellular adenosine. J Neurosci 1999;19: 1932–1939.
65. Qu L, Leung LS. Mechanisms of hyperthermia-induced depression of GABAergic synaptic transmission in the immature rat hippocampus. J Neurochem 2008;106: 2158–2169.
66. Capogna M, Gahwiler BH, Thompson SM. Presynaptic enhancement of inhibitory synaptic transmission by protein kinases A and C in the rat hippocampus *in vitro*. J Neurosci 1995;15:1249–1260.
67. Chiles WD. Effects of elevated temperature on performance of a complex mental task. Ergonomics 1958;2:89–96.
68. Bell CR, Provins KA, Hiorns RW. Visual and auditory vigilance during exposure to hot and humid conditions. Ergonomics 1964;7:279–288.
69. Poulton EC, Kerslake MB. Initial stimulating effect of warmth upon perceptual efficiency. Aerospace Med 1965; 36:29–32.
70. Lovingood BW, Blyth CS, Peacock WH, Lindsay RB. Effects of d-amphetamine sulfate, caffeine and high temperature on human performance. Res Quart 1967;38:64–71.
71. Colquhoun WP. Effects of raised ambient temperature and event rate on vigilance performance. Aerospace Med 1969; 40:413–417.
72. Colquhoun WP, Goldman RF. Vigilance under induced hyperthermia. Ergonomics 1972;15:621–632.
73. Nunneley SA, Dowd PJ, Myhre LG, Stribley RF, McNee RC. Tracking-task performance during heat stress simulating cockpit conditions in high-performance aircraft. Ergonomics 1979;22:549–555.
74. Kobrick JL, Fine BJ. Climate and human performance. In: Oborne DJ, Gruneberg MM, editors. The physical environment at work. Chichester: Wiley Press; 1983. pp 69–107.
75. Enander AE. Effects of thermal stress on human performance. Scand J Work Environ Health 1989;15(Suppl. 1):27–33.
76. Enander AE, Hygge S. Thermal stress and human performance. Scand J Work Environ Health 1990; 16(Suppl. 1):44–50.
77. Ramsey JD. Working safely in hot environments. In: Das B, editor. Advances in industrial ergonomics and safety II. London: Taylor & Francis; 1990. pp 889–896.
78. Ramsey JD. Task performance in heat: A review. Ergonomics 1995;38:154–165.
79. Grether WF. Human performance at elevated environmental temperatures. Aerospace Med 1973;44:747–755.
80. Ramsey JD, Morrissey SJ. Isodecrement curves for task performance in hot environments. Appl Ergon 1978;9:66–72.
81. Hancock PA. Heat stress impairment of mental performance: A revision of tolerance limits. Aviat Space Environ Med 1981;52:778–784.
82. Hancock PA. Task categorizations and the limits of human performance in extreme heat. Aviat Space Environ Med 1982;53:778–784.
83. Ramsey JD, Kwon G. Recommended alert limits for perceptual motor loss in hot environments. Int J Indust Ergon 1992;9:245–257.
84. Hancock PA, Vasmatzidis I. Human occupational and performance limits under stress: The thermal environment as a prototypical example. Ergonomics 1998;4:1169–1191.
85. Hancock PA, Vasmatzidis I. On the behavioral basis for stress exposure limits: The foundational case of thermal stress. In: Karwowski W, Marras WS, editors. The occupational ergonomics handbook. Boca Raton, Florida: CRC Press; 2000. pp 1707–1739.
86. Amos D, Hansen R, Lau WM, Michalski JT. Physiological and cognitive performance of soldiers conducting routine patrol and reconnaissance operations in the tropics. Mil Med 2000;165:961–966.
87. Cian C, Barraud PA, Melin B, Raphel C. Effects of fluid ingestion on cognitive function after heat stress or exercise induced dehydration. Int J Psychophysiol 2001;42: 243–251.
88. McMorris T, Swain J, Smith M, Corbett J, Delves S, Sale C, Harris RC, Potter J. Heat stress, plasma concentrations of adrenaline, noradrenaline, 5–hydroxytryptamine and cortisol, mood state and cognitive performance. Internat J Psychophysiol 2006;61:204–215.
89. Wyon DP, Andersen I, Lundqvist GR. The effects of moderate heat stress on mental performance. Scand J Work Environ Health 1979;5:352–361.
90. Kenney MJ, Fels RJ. Forebrain and brain stem neural circuits contribute to altered sympathetic responses to heating in senescent rats. J Appl Physiol 2003;95:1986–1993.
91. Hancock PA. The effect of skill on performance under an environmental stressor. Aviat Space Environ Med 1986;57:59–64.
92. Allan JR, Gibson TM. Separation of the effects of raised skin and core temperature on performance of a pursuit rotor task. Aviat Space Environ Med 1979;50:678–682.
93. Allan JR, Gibson TM, Green RG. Effect of induced cyclic changes of deep body temperature on task performances. Aviat Space Environ Med 1979;50:585–589.
94. Gibson TM, Allan JR. Effect on performance of cycling deep body temperature between 37.0 and 37.6°C. Aviat Space Environ Med 1979;59:935–938.
95. Gibson TM, Allan JR, Lawson CJ, Green RG. Effect of induced cyclic changes of deep body temperature on performance of a flight simulator. Aviat Space Environ Med 1980;51:356–360.
96. Pepler RD. Warmth and performance: An investigation in the tropics. Ergonomics 1958;2:63–88.
97. Vasmatzidis I, Schlegel RE, Hancock PA. An investigation of heat stress effects on time-sharing performance. Ergonomics 2002;45:218–239.
98. Hancock PA, Vasmatzidis I. Effects of heat stress on cognitive performance: The current state of knowledge. Int J Hyperthermia 2003;19:355–372.
99. Nybo L, Secher NH, Nielsen B. Inadequate heat release from the human brain during prolonged exercise with hyperthermia. J Physiol 2002;545:697–704.
100. Hancock PA. Sustained attention under thermal stress. Psychol Bull 1986;99:263–281.
101. Pilcher JJ, Nadler E, Busch C. Effects of hot and cold temperature exposure on performance: A meta-analytic review. Ergonomics 2002;45:682–698.
102. Pud D, Sapir S. The effects of noxious heat, auditory stimulation, a cognitive task, and time on task on pain perception and performance accuracy in healthy volunteers: A new experimental model. Pain 2006;120:155–160.
103. Bhalang K, Sigurdsson A, Slade GD, Maixner W. Association among four modalities of experimental pain in women. J Pain 2005;6:604–611.
104. Edwards RR, Fillingrim RB. Self-reported pain sensitivity: Lack of correlation with pain threshold and tolerance. Eur J Pain 2007;11:594–598.
105. Mündel T, Hooper PL, Bunn SJ, Jones DA. The effects of face cooling on the prolactin response and subjective comfort

during moderate passive heating in humans. Exp Physiol 2006;91:1007–1014.
106. Simmons SE, Saxby BK, McGlone FP, Jones DA. The effect of passive heating and head cooling on perception, cardiovascular function and cognitive performance in the heat. Eur J Appl Physiol 2008;104:271–280.
107. Racinais S, Gaoua N, Grantham J. Hyperthermia impairs short-term memory and peripheral motor drive transmission. J Physiol 2008;586:4751–4762.
108. Todd G, Butler JE, Taylor JL, Gandevia SC. Hyperthermia: A failure of the motor cortex and the muscle. J Physiol 2005;563:621–631.
109. Dewhurst S, Riches PE, Nimmo MA, De Vito G. Temperature dependence of soleus H-reflex and M wave in young and older women. Eur J Appl Physiol 2005;94: 491–499.
110. Reilly JP. Applied bioelectricity: From electrical stimulation to electropathology. New York: Springer; 1998.
111. D'Andrea JA, Adair ER, John O, de Lorge JO. Behavioral and cognitive effects of microwave exposure. Bioelectromagnetics 2003(Suppl 6):S39–S62.
112. Gandhi OP. Polarization and frequency effects on whole animal energy absorption of RF energy. Proc IEEE 1974;62:1171–1175.
113. Mickley A, Cobb BL, Mason P, Farrell S. Disruption of a putative working memory task and selective expression of brain *c-fos* following microwave-induced hyperthermia. Physiol Behav 1994;55:1029–1038.
114. Mickley A, Cobb BL, Mason P, Farrell S. Thermal tolerance reduces hyperthermia-induced disruption of working memory: A role for endogenous opiates? Physiol Behav 1998;63:855–865.
115. D'Andrea JA, Gandhi OP, Lords JL. Behavioral and thermal effects of microwave radiation at resonant and non-resonant wavelengths. Radio Sci 1977;12:251–256.
116. de Lorge JO, Ezell CS. Observing responses of rats exposed to 1.28 and 5.62 GHz microwaves. Bioelectromagnetics 1980;1:183–198.
117. Thomas JR, Schrot J, Banvard RA. Comparative effects of pulsed and continuous-wave 2.8 GHz microwaves on temporally defined behavior. Bioelectromagnetics 1982;3: 227–235.
118. de Lorge JD. The thermal basis for disruption of operant behavior by microwaves in three animal species. In: E.R. Adair (ed.), Microwaves and thermoregulation. New York: Academic Press: 1983, pp 379–399.
119. de Lorge JO. Operant behavior and colonic temperature of rhesus monkeys, *Macaca mulatta*, exposed to microwaves at frequencies above and near whole body resonance. Bioelectromagnetics 1984;5:233–246.
120. Lebovitz RM. Pulse modulated and continuous wave microwave radiation yield equivalent changes in operant behavior of rodents. Physiol Behav 1983;30:891–898.
121. D'Andrea JA, Thomas A, Hatcher DJ. Rhesus monkey behavior during exposure to high-peak-power 5.62 GHz microwave pulses. Bioelectromagnetics 1994;15:63–176.
122. Burr JG, Krupp JH. Real-time measurement of RFR energy distribution in the *Macaca mulatta* head. Bioelectromagnetics 1980;1:21–34.
123. Stern SL. Behavioral effects of microwaves. Neurobehav Toxicol 1980;2:49–58.
124. D'Andrea JA. Behavioral evaluation of microwave irradiation. Bioelectromagnetics 1999;20:64–74.
125. Yamaguchi H, Tsurita G, Ueno S, Watanabe S, Wake K, Taki M, Nagawa H. 1439 mHz pulsed TDMA fields affect performance of rats in a T-maze task only when body temperature is elevated. Bioelectromagnetics 2003;24: 223–230.
126. Cobb BL, Jauchem JR, Adair ER. Radial arm maze performance of rats following repeated low level microwave radiation exposure. Bioelectromagnetics 2004;25:49–57.
127. Xu Z-W, Hou B, Li Y-F, Gao Y, Su Z-T, Yang G-S, Zhao S-F, He F-C, Zhang C-G. Theophylline attenuates microwave-induced impairment of memory acquisition. Neurosci Lett 2007;412:129–133.
128. Kumlin T, Iivonen H, Miettinen P, Juvonen A, van Groen T, Puranen L, Pitkäaho R, Juutilainen J, Tanila H. Mobile phone radiation and the developing brain: Behavioral and morphological effects in juvenile rats. Radiation Res 2007;168:471–479.
129. Preece A, Iwi G, Davies-Smith A, Wesnes K, Butler S, Lim E, Varey A. Effect of a 915 MHz simulated mobile phone signal on cognitive function in man. Int J Radiat Biol 1999;75:447–456.
130. Koivisto M, Krause C, Revonsuo A, Laine M, Hämäläinen H. The effects of electromagnetic field emitted by GSM phones on working memory. NeuroReport 2000; 11:1641–1643.
131. Koivisto M, Revonsuo A, Krause C, Haarala C, Sillanmäki L, Laine M, Hämäläinen H. Effects of 902 MHz electromagnetic field emitted by cellular telephones on response times in humans. NeuroReport 2000;11:413–415.
132. Edelstyn N, Oldershaw A. The acute effects of exposure to the electromagnetic field emitted by mobile phones on human attention. NeuroReport 2001;13:119–121.
133. Lee TMC, Ho SMY, Tsang LYH, Yang SYC, Li LSW, Chan CCH. Effect on human attention of exposure to the electromagnetic field emitted by mobile phones. NeuroReport 2001;12:729–731.
134. Hamblin DL, Wood AW. Effects of mobil phone emissions on human brain activity and sleep variables. Int J Radiat Biol 2002;78:659–669.
135. Krause CM, Sillanmäki L, Koivisto M, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H. Effects of electromagnetic field emitted by cellular phones on the EEG during a memory task. NeuroReport 2000;11: 761–764.
136. Krause CM, Haarala C, Sillanmäki L, Koivisto M, Alanko K, Revonsuo A, Laine M, Hämäläinen H. Effects of electromagnetic field emitted by cellular phones on the EEG during an auditory memory task: A double blind replication study. Bioelectromagnetics 2004;25:33–40.
137. Haarala C, Björnberg L, Ek M, Laine M, Revonsuo A, Koivisto M, Hämäläinen H. Effect of a 902 MHz electromagnetic field emitted by mobil phones on human cognitive function: A replication study. Bioelectromagnetics 2003; 24:283–288.
138. Haarala C, Ek M, Björnberg L, Laine M, Revonsuo A, Koivisto M, Hämäläinen H. 902 MHz mobile phone does not affect short term memory in humans. Bioelectromagnetics 2004;25:452–456.
139. Eliyahu I, Luria R, Hareuveny R, Margaliot M, Meiran N, Shani G. Effects of radiofrequency radiation emitted by cellular telephones on the cognitive functions of humans. Bioelectromagnetics 2006;27:119–126.
140. Luria R, Ilan Eliyahu I, Hareuveny R, Margaliot M, Meiran N. Cognitive effects of radiation emitted by cellular phones: The influence of exposure side and time. Bioelectromagnetics 2009;30:198–204.
141. Wiholm C, Lowden A, Kuster N, Hillert L, Arnetz BB, Åkerstedt T, Moffat SD. Mobile phone exposure and spatial memory. Bioelectromagnetics 2009;30:59–65.
142. Hutter H-P, Moshammer H, Wallner P, Kundi M. Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. Occup. Environ. Med. 2006;63:307–313.

143. Oftedal G, Straume A, Johnsson A, Stovner LJ. Mobile phone headache: A double blind, sham-controlled provocation study. Cephalalgia 2007;27:447–455.
144. Abdel-Rassoul G, Abou El-Fateh O, Abou Salem M, Michael A, Farahat F, El-Batanouny M, Salem E. Neurobehavioral effects among inhabitants around mobile phone base stations. NeuroToxicology 2007;28:434–440.
145. Duffy E. The concept of energy mobilization. Psych Rev 1951;58:30–40.
146. Duffy E. The psychological significance of the concept 'arousal' or 'activation'. Psych Rev 1957;64:621–632.
147. Hebb DO. Drives and the C.N.S. (Conceptual Nervous System). Psych Rev 1955;62:243–254.
148. Näätänen R. The inverted-U relationship between activation and performance: A critical review. In: Kornblum S, editor. Attention and performance IV. New York: Academic Press; 1973. pp 155–174.
149. Pribram KH, McGuiness D. Arousal, activation and effort in the control of attention. Psych Rev 1975;82:116–149.
150. Hancock PA. Arousal theory, stress and performance: Problems of incorporating energetic aspects of behavior onto human-machine systems function. In: Mark, L.S. Warm, J.S. Huston R.L. (eds.), Ergonomics and human factors: Recent research. New York: Springer-Verlag: 1987, pp 170–179.
151. Hancock PA. Environmental stressors. In: Warm JS, editor. Sustained attention in human performance. New York: Wiley Press; 1984. pp 103–142.
152. Hancock PA, Warm JS. A dynamic model of stress and sustained attention. Hum Fact 1989;31:519–537.