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Motion sickness, nausea and thermoregulation: The "toxic" hypothesis

Eugene Nalivaiko[1,*], John A Rudd[2], and Richard HY So[3]

[1]School of Biomedical Sciences and Pharmacy; University of Newcastle; Callaghan, NSW, Australia; [2]School of Biomedical Sciences; Chinese University of Hong Kong, Shatin; Hong Kong, China; [3]Division of Biomedical Engineering; the Hong Kong University of Science and Technology; Hong Kong, China

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Abbreviations: MS, motion sickness; ACTH, adrenocorticotropic hormone; SCL, skin conductance level.

Principal symptoms of motion sickness in humans include facial pallor, nausea and vomiting, and sweating. It is less known that motion sickness also affects thermoregulation, and the purpose of this review is to present and discuss existing data related to this subject. Hypothermia during seasickness was firstly noted nearly 150 years ago, but detailed studies of this phenomenon were conducted only during the last 2 decades. Motion sickness-induced hypothermia is philogenetically quite broadly expressed as besides humans, it has been reported in rats, musk shrews and mice. Evidence from human and animal experiments indicates that the physiological mechanisms responsible for the motion sickness-induced hypothermia include cutaneous vasodilation and sweating (leading to an increase of heat loss) and reduced thermogenesis. Together, these results suggest that motion sickness triggers highly coordinated physiological response aiming to reduce body temperature. Finally, we describe potential adaptive role of this response, and describe the benefits of using it as an objective measure of motion sickness-induced nausea.

Introduction

Principal symptoms of motion sickness (MS) in humans include facial pallor, nausea and vomiting, and sweating; these are accompanied by gastric awareness and discomfort. Among biochemical markers, a relatively specific physiological measurement is the increases in plasma vasopressin accompanied by non-specific rises in plasma ACTH, cortisol and catecholamines (see[1] for a more detailed review). Although sweating has been a common symptom of MS, thermoregulation-related measurements have not been part of the mainstream assessment of MS as compared with subjective ratings (e.g., rated nausea[2] and Simulator Sickness Questionnaire[3]). The purpose of this review is 3-fold: (i) to present and discuss existing data relating thermoregulation and MS leading to identification of research gaps; (ii) to address the 'where' and 'why' questions related to MS-induced thermoregulatory changes (the toxic hypothesis); and (iii) to highlight the benefits of thermoregulation-based bio-markers for the study of MS among human and animals. We initially present a critical review of studies examining hypothermic effects of MS in humans and animals; this is followed by a review of studies that provide mechanistic insight into how MS induces hypothermia: this includes cutaneous vasodilation, sweating and thermogenesis. Gaps in the current knowledge are identified. The potential sites of interaction where nausea-related neural pathways may affect thermoregulatory pathways are explored. The discussion focuses on potential sites of interaction between pathways and considers how such interactions take place during MS.

General overview of association between motion sickness and hypothermia

A causative link between MS and reductions of core body temperature has been documented in a number of studies. To the best of our knowledge, the first report of this phenomenon was made by Hess[4] who noted that in subjects experiencing seasickness, body temperature dropped by about half a degree. Likewise, Ogata[5] reported that during a long sea voyage, his body temperature was lower on the days of rough sea, when he experienced nausea, compared to normal days. Several experimental studies of MS also noted this phenomenon,[6,7] although they were not designed to specifically focus on temperature changes.

At the beginning of last decade, several interrelated investigations were specifically designed by Canadian and Swedish Defense research institutions to assess combined effects of provocative motion and hypothermia. All of them used similar experimental paradigm – induction of MS by means of pseudo-Coriolis intervention (rotation of a subject sitting in a chair

*Correspondence to: Eugene Nalivaiko; Email: Eugene.nalivaiko@newcastle.edu.au
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around a vertical axis, with periodically repeated head tilts) followed by immersion in a pool of cold or cool water. The first of these studies found that MS potentiated hypothermia induced by water immersion.[8] -Four follow up studies confirmed this finding.[9-12] Overall, the difference in the rectal temperature changes between subjects experiencing MS and control subjects reached 0.3–0.4°C. More recently, it was reported that MS-related hypothermia requires neither water immersion nor cool environment, and could be elicited in a thermoneutral conditions, with air temperature 28–29°C (**Fig. 1**).[13] It is worth noting that in all cited human experiments, the hypothermic effect of MS lasted well beyond the duration of subjective symptoms of MS.

Preclinical studies using the rat, which is incapable of emesis, noted that provocative motion could induce hypothermia.[14] However, the temperature measurements were performed using rectal probes, with just 2 time points. This phenomenon was recently reproduced and examined in detail in 2 animal studies that employed biotelemetry.[15,16] Rats equipped with telemetric transmitters for measuring temperature in the abdominal cavity were subjected to rotation (at 45 rpm) around vertical axis in their home cages. This resulted in a fall in their core temperature by about 1.5°C during 40-min provocation; temperature started to recover to the basal level shortly after the end of rotation. Similar effects were seen in a house musk shrew (*Suncus murinus*) – an insectivore possessing vomiting reflex.[15] MS in this case was induced by reciprocating linear motion (4 cm, 1 Hz, for 10 min), and a fall in body temperature in the interscapular and lumbar regions coincided with retching and vomiting episodes, and it is possible that animals could experience nausea-like sensations at this time. It thus appears that hypothermia induced by provocative motion is a broad biological phenomenon as it could be reliably reproduced in 3 mammalian species – humans, rats and shrews. We have recently confirmed that it is also present in mice (unpublished observation).

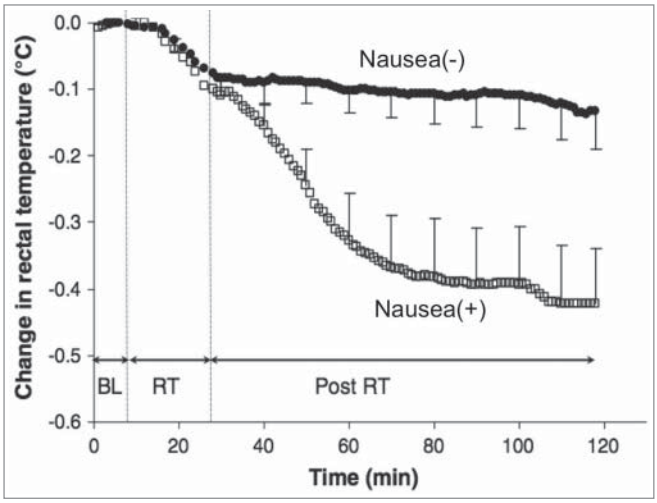

Figure 1. Motion sickness facilitated body cooling in human volunteers. Rectal temperature was recorded at the baseline (BL), during rotation (RT) and after rotation (Post RT). Rotation was performed while sitting undressed in a chair in a thermoneutral environment (28–29°C), with incrementing angular speed (from 10° s^{-1} to 150° s^{-1}). The only difference between control (Nausea(−)) and motion sickness (Nausea(+)) conditions was the instruction to tilt head during rotation; this intervention reliably produced nausea. Note that initial small temperature fall during rotation was similar in both conditions; authors explained it by an increased move of air. From,[13] with permission.

Motion sickness and thermoregulatory behavior

While a sensation of body warmth and a desire for fresh (cool) air may be common observation among those who experienced MS, only one study specifically addressed and documented this phenomena.[13] It was conducted in a thermoneutral environment (28-29°C), where MS was provoked by pseudo-Coriolis intervention; subjects separately rated their nausea, perception of temperature, and their thermal comfort/discomfort. Prior to the provocation, ratings indicated that the environment was perceived as comfortable and neutral or slightly warm; and at the end of provocation, when all subjects experienced intense nausea, the ambient temperature was perceived as uncomfortable and too warm. These distorted sensations were paradoxical, as core body temperature actually *fell* during and after the provocation, suggesting that a distortion occurred in the physiological mechanisms responsible for the conscious perception of sensory information from body thermoreceptors. It is obvious that such distorted temperature sensation in subjects with MS could motivate and induce cold-seeking thermoregulatory behavior.

In a cited above rodent study,[15] no effect of provocative motion on the preferred ambient temperature was found; however temperature preference could be assessed only after the termination of the provocation, due to technical reasons. It is thus remains unknown whether provocative stimuli cause behavioral thermoregulatory effects in species others than humans.

Motion sickness and sweating

Sweating is a well recognized symptom of the MS,[3] and its quantitative assessment was performed in a number of studies. In the current section we initially focus on several relevant methodological issues; this is followed by a summary of results obtained in the previous studies. The latter are grouped by i) provocative stimulation; and ii) correlation of the sweating data with the subjective rating of MS.

Studies discussed below employed one of 2 different methods for assessing sweating – detection of MS-induced changes in skin conductance that is dependent on the activity of sweat glands, and a direct assessment of changes in sweating rate. The former approach (termed skin galvanic response or skin conductance level, SCL) is based on measuring skin resistance/conductance by passing a low-intensity constant current between 2 electrodes attached to the skin. In contrast, sweating rate detection is based on assessing changes in the content of water vapor in the dehumidified air flushed through a capsule attached to the skin. It is surprising that the first paper reporting a direct methodical comparison of both methods has just appeared.[17] Its results are highly relevant to this review. Sweating was elicited by a whole-body thermal stimulus, and after reaching temperature threshold for sweating, only a fall in skin resistance was initially observed, whereas changes in sweat rate occurred after a delay of several

minutes. This difference is not due to low sensitivity of sweating rate detection but is explained by the physiology of sweating: prior to appearing on the surface of the skin, primary sweat must fill the ducts of the sweat glands and overcome the elastic resistance of their walls. Furthermore, its secretion rate should exceed the rate of reabsorption in the ducts, so that the secondary sweat is released from the duct opening after a delay compared to the onset of secretion. As a result, there is a delay between the fall in skin resistance (initially mediated by filling the ducts with concentrated electrolyte) and an increase in humidity of the air in the proximity of the skin surface. These results are in good accord with earlier work where a similar delay between rise in SCL and sweating rate was found during provocative motion.[18] Consequently, measurements of SCL appear to be a more sensitive approach for the detection of the sweating response.

The second methodological issue related to the instrumental assessment of sweating is the location of sensors. SCL recorded from fingers (the most common location of electrodes) is highly sensitive to arousing/stressful stimuli; it is broadly used in psychophysiology and known as the galvanic skin response, or GSR. In contrast, the less commonly recorded dorsum of the hand or forehead areas appear to be less sensitive to such stimuli. In the only study where SCL was simultaneously recorded from both palmar and dorsal sides of the hand during provocative motion, conductance increased at both sites but with different latencies: while palmar ("stress") responses occurred simultaneously with the onset of head movements during rotation, dorsal ("thermal") responses developed only few minutes later, and coincided with the onset of nausea.[19] It thus appears that location of electrodes for SCL recordings must match the purpose of a MS study, with finger location more suitable for assessing stress/arousal levels, and forehead – for assessing sweating rate (see below).

One more methodological aspect related to SCL detection in MS studies is whether phasic (transient) or tonic responses should be quantified. Golding[18] specifically addressed this issue, with SCL recorded during provocative motion from either finger or forehead, and with subsequent correlation of phasic and tonic responses from both regions to the nausea score. It appeared that phasic changes in the forehead (in peaks/min) had the highest correlation, and tonic changes in the finger – the lowest. In the subsequent study by[20] this finding was confirmed; a very impressive **Figure 2** from this paper documents lack of provocative motion-induced changes in ongoing SCL peaks recorded from the finger but a dramatic increase in the incidence of such peaks in the forehead area at the time of high rating of nausea. The differential sensitivity between forehead and finger sites to MS-inducing stimulation was also reported by 2 independent studies[21,22]

Most experimental works where effects of MS on sweating were studied used provocative motion – either linear accelerations/decelerations, or pseudo-Coriolis provocation. The first study, where rise in SCL was observed during MS provocation, was conducted by Hemingway[6] in 1944. An increase of sweating rate was confirmed as an increase in the weight of capsules with dehumidified calcium anhydrite that were attached to the skin. Subsequently, rise in finder tonic SCL was confirmed.[18,19,23-25] Provocative motion leading to nausea also robustly increased the sweating rate in the forehead.[8,11,13]

The first study of visually-induced MS by Parker[26] used playback of a film that was captured from a car driving on a winding road. Measurements of SCL enabled the discrimination of MS-susceptible individuals from MS-resistant individuals. These findings were reproduced (with a different visual stimulus).[22] A rise in SCL has been reported during another common MS provocation - optokinetic stimulation (movement of black/white vertical strips in a visual field).[21,27-29]

One of the authors of the present paper has recently tested the hypothesis that nausea rating and symptoms of sweating would be correlated. Twelve participants (6 male and 6 female) were exposed to a 30 minute rotating drum pattern (vertical black and white stripes projected to a panoramic screen). The original objective of the study was to examine the effects of eye movements on motion sickness and sweating was measured as one of the standard dependent variable.[30]

During the exposure, rated nausea levels were measured every 2 minutes using a 7-point nausea scale.[2] Before and after the exposure, all participants filled in a set of simulator sickness questionnaire.[3] Results of the 12 participants indicated that the nausea rating correlated significantly with the levels of sweating as measured by the questionnaire ($r = 0.67$, $P < 0.01$). This suggests that symptoms of nausea and sweating go hand in hand during visually-induced motion sickness.

A number of studies focusing on simulator sickness or virtual reality-induced motion sickness reported rise in tonic SCL associated with MS.[31,32] Others did not observe changes in SCL in subjects experiencing simulator sickness.[33] This was probably due to relatively mild MS symptoms and by the fact that only tonic level was measured with electrodes attached to the palmar surface of the fingers – the least sensitive experimental configuration (see above). Besides physical and visual stimuli, dizziness or nausea are common effect of caloric ear stimulation – an otonerological test for assessing the integrity of vestibular function. Cui et al.[34] reported that subjects experiencing nausea during caloric ear stimulation also exhibit increases in tonic skin conductance in fingers and in sweating rate on the forehead.

Some of the cited above studies were able to discriminate MS-susceptible from MS-resistant individuals[6,22,26] while others specifically aimed to determine whether there is a correlation between subjectively perceived nausea and associated changes in physiological parameters, including skin conductance levels. Such correlation was found,[18,21,25,27,28] with the highest correlation (0.62) being between phasic SCL changes in the forehead and MS rating. Negative results[23] were most likely due to the location of electrodes in this study on the fingers (see above).

Motion sickness and cutaneous vasodilation

Heat loss through skin is a major thermoregulatory mechanism in mammals possessing reasonable areas of glabrous skin with developed arterio-venous anastomoses. Dilation of these anastomoses allows a substantial amount of warm blood to get in close proximity with the ambient air to dissipate heat in sub-thermoneutral environment. Conversely, constriction of superficial

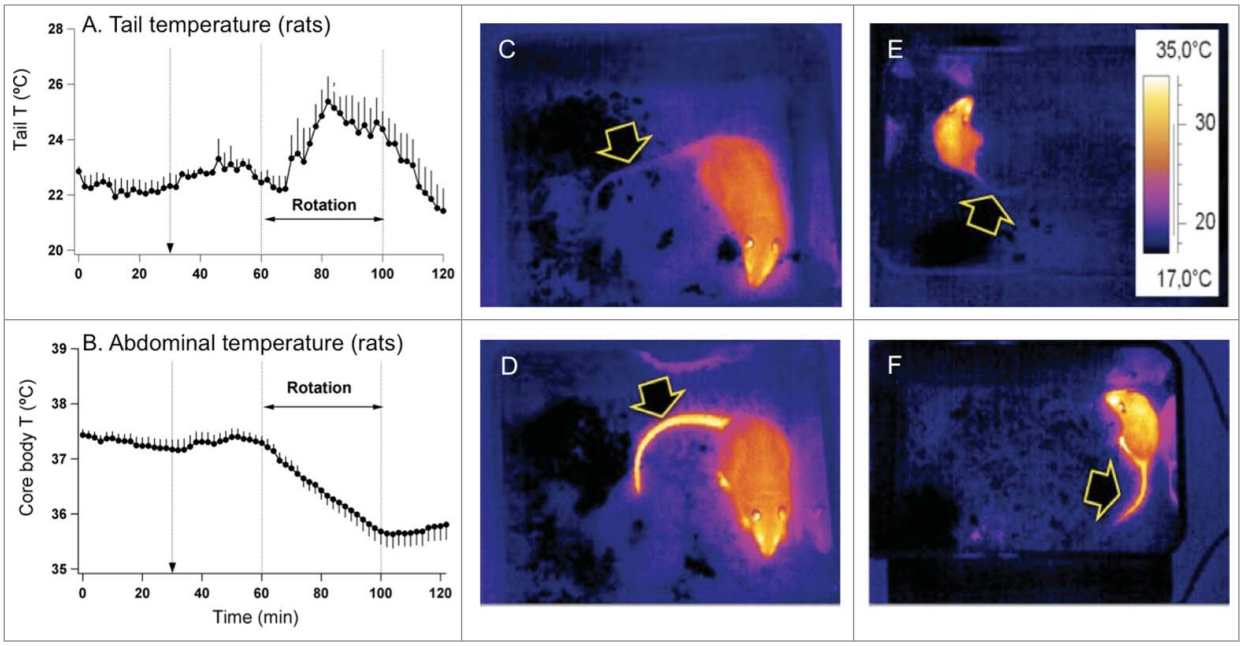

Figure 2. In rats and mice, provocative motion causes hypothermia that is mediated by heat loss due to vasodilation in the thermoregulatory tail vascular bed. (**A**) Changes in the tail temperature in rats that were determined by means of infrared imaging; (**C and D**) present 2 images of a rat taken just before (**C**) and 20 min after the onset of provocative motion (**D**). (**C**) Fall in the core (abdominal) temperature induced by a provocative motion; telemetric recordings. Note that tail vasodilation preceded hypothermia. Similar effects were observed in mice (**E**) before provocation; (**F**) during provocation). In rats, the provocation was a rotation in a home cage at 45 rpm; in mice—placing them in their home cages on an orbital laboratory shaker (1 Hz, 4-cm circular motion). Inset in (**E**) shows temperature coding in pseudo-colors. (**A–D**) Modified from Ref.[15]; (**E and F**) unpublished observation.

skin vessels leads to heat conservation. Existing human data on the link between motion sickness and cutaneous vascular tone are controversial, limited and inconclusive. The first study where skin blood flow was assessed during MS provocation, reported a 50-60% fall in finger pulse volume indicative of vasoconstriction.[7] Several other early studies demonstrated that MS is associated with an increase in forearm blood flow.[35,36] However, they were conducted by means of venous occlusion plethysmography (a method based on the volume changes in the forearm), and thus could not determine whether blood flow increased in the skin or in the muscles of the forearm. Using the difference between forearm and finger temperature as a surrogate measure of cutaneous vascular tone, Nobel and colleagues concluded that MS attenuates cutaneous vasoconstriction provoked by immersion in the cold water.[10,11] A transient vasodilation in the forearm and calf during MS provocation has been reported in a study employing direct measurement of cutaneous blood flow by laser Doppler.[9] Interestingly, in the Cheung's study, cutaneous blood flow remained unchanged in 2 subjects who did not report nausea. Overall, further experiments are definitely required to verify and describe the link between nausea and cutaneous vascular tone in humans.

In contrast to human studies, our recent animal experiments, conducted in 3 different laboratories, revealed that provocative motion (rotation around vertical axis at 45 rpm) causes a very robust vasodilatory response in rat cutaneous (tail) vascular bed.[15] Tail temperature started to rise within several minutes of provocation, peaked at about 20 min, and then returned to the baseline. We subsequently reproduced similar effects in mice (unpublished observation). Since rats and mice do not have vomiting reflex, it is difficult to link cutaneous vascular effects observed in these species to a "nausea-like" state. It however appears that identical response could be elicited by provocative motion in *Suncus murinus*, an insectivore possessing vomiting reflex.[15] Importantly, in *Suncus murinus* tail vasodilation occurred prior to retching/vomiting episodes; thus, if these animals experience sensations similar to human nausea prior to the onset of vomiting, tail vasodilation may be related to the nausea-like state too.

Motion sickness and thermogenesis

Only few studies questioned whether motion sickness affects thermogenesis in humans. For assessing this function, researchers employed indirect calorimetry – measurement of the minute volume of consumed O_2 (VO_2) that directly reflects changes in heat production. In the initial work,[8] after MS provocation or corresponding control periods, subjects were immersed in a pool with warm (28°C) water; this resulted in about 2-fold increase in VO_2 during 90 min of immersion, without any difference between MS and control conditions. In subsequent work, the same research group found that cold-induced VO_2 rise was reduced by MS provocation,[10] and argued that this difference was due to the temperature of the water during immersion, such that the larger increase in thermogenesis represented larger substrate for MS-

induced effects. This appears quite plausible providing that in this second study, with water temperature of 15°C, the rise of VO_2 was more than 4-fold. However, in another follow-up study, where the water temperature during immersion was also 15°C, no effects of motion provocation on VO_2 were seen.[11] Here, authors offered a potential explanation for the discrepancy: in their 2006 study, where the effects of MS were present, in addition to psedo-Coriolis MS provocation prior to immersion, subjects were exposed to the optokinetic drum stimulation during the immersion to maintain the MS at steady state. Thus it may be that thermogenesis is affected mainly during, but not after provocative stimulation.

In summary, published human data suggest that even if MS affects cold-induced thermogenesis, these effects are relatively minor. Also, indirect calorimetry did not allow to determine whether MS affected shivering or non-shivering thermogenesis as a electromyogram was not recorded in the cited studies. There are currently no animal data on the link between MS and thermogenesis, and this gap of knowledge awaits further experimentation.

Where motion sickness could interfere with temperature control?

We believe that answering this question will shed light on the poorly understood neural substrate of nausea. During the last decade, it became apparent that some drugs that efficiently suppress vomiting, have only moderate effects against nausea.[37,38] This differential action on nausea vs. vomiting led to the realization that there may be different pathways and control systems for nausea and emesis. Indeed, evidence suggests the essential neural circuitry for vomiting reflex is within the lower brainstem,[1] and emesis could be elicited in decerebrated animals.[39] Consequently, a search for the neural substrate of nausea must be focused on the supra-medullary level. There is currently only one human brain imaging studies of nausea.[40] Visually-induced nausea was associated with cortical activation in the prefrontal areas responsible for emotional processing and the insula (responsible for conscious interoceptive awareness); subcortical regions included amygdala, striatum and dorsal pons. In animals, brain activation could be assessed by immunohistochemical detection of Fos protein. A straightforward approach for identifying nausea-related brain regions in animals would be to compare where there is an overlap between chemically- and vestibularly-activated brain sites. Such animal data for *chemical* activation are available, with consistent activation, at the supra-medullary level, of the amygdala, the bed nucleus of stria terminalis, several hypothalamic regions including paraventricular, and the parabrachial nucleus.[41-43] Animal Fos data following *vestibular* stimulation partially confirm these findings.[44] It therefore appears that the missing parts of the puzzle are identification of subcortical area(s) through which sensory information responsible for the development of MS reaches forebrain areas where nausea is perceived. It is not unreasonable to suggest that following detection of sensory mismatch – a principal mechanism postulated by the current theory of MS – relevant neural signal ascend to the cortical structures and at the same time reach autonomic centers, presumably in the brainstem, to trigger bodily responses, including thermoregulation, that accompany MS.

Critical analysis of the previously presented sections clearly demonstrates that MS is associated with a highly coordinated thermoregulatory response aiming to reduce the core body temperature by cognitive/behavioral (preference for cooler environment) and autonomic (sweating, reduced skin vasoconstriction and possibly reduced thermogenesis) means. While the physiological significance of this response is not known, it may have an important consequence for nausea research. Neural pathways for thermoregulatory control have been elucidated in great detail during last decade (see[45-47] for reviews), and their functional architecture could be summarized as following: information from central (brain) and peripheral thermosensors is integrated in the preoptic anterior hypothalamus that sends excitatory projection to the dorsomedial hypothalamus, a major integrative center for autonomic output. From there, descending presympathetic pathways project to the medullary raphe/parapyramidal area and then to the intermedolateral column of the spinal cord, where separate populations of sympathetic neurones control 2 thermoeffectors – brown adipose tissue responsible for non-shivering thermogenesis and cutaneous vascular bed responsible for heat dissipation Descending pathways that control sweating are less known, but their final central neurones must be also located in the spinal sympathetic areas. It is thus clear that there are a limited number of neural targets where neural signals generated by MS could interfere with the descending thermoregulatory pathways. The fact that MS induces changes in subjective perception of ambient temperature and preference for a cooler environment[13] indicates that this interference occurs quite high in the neuraxis. Functional analysis of afferent input to this brain structure thus might be a fruitful approach to elucidate where in the brain occurs the sensory mismatch leading to MS.

Why motion sickness causes integrative hypothermic response?

Compelling evidence presented in the previous sections suggests that MS triggers coordinated cognitive, behavioral and physiological changes that act synergistically to cool down the body. In fact, it is quite remarkable that seemingly all available bodily resources are mobilized for this purpose: changed perception of and preference for ambient temperature, sweating, dilatation of cutaneous vasculature and reduced thermogenesis. While not all these changes have been documented in all studied species, the overall hypothermic effect appears to be quite robust, and is present in mice, musk shrews, rats and humans. The obvious questions that now arise are *why* this hypothermic effect develops, or, in other words, what is its physiological significance, and how did it developed. With regard to the latter issue, there is no evidence for any evolutionary advantage for the appearance of this reaction. Furthermore, there were no relevant stimuli in the history of evolution. Indeed, it is hard to imagine how terrestrial animals (except humans) could be subjected to rotational or oscillatory linear provocative motion, or to any kind of provocative visual stimulation. Even in humans, there were no relevant

natural or artificial provocations prior to the beginning of sea voyages; one could speculate that there were some traditional tribal dances (akin to Sufi whirling – a form of Islamic physically active meditation,[48] but it is difficult to imagine that they could have major influences on the physiological response that we discuss. Consequently, it seems that MS-related hypothermia is not a product of evolutionary pressure; this is however not to say that it has no adaptive physiological significance.

It may be that potential answer to the "why" and "how" question could be found by comparing MS-induced hypothermia with hypothermic responses produced by other means. If we exclude pharmacologically- and cold-induced hypothermia, the only other situation when it occurs in response to environmental stressors, both in humans[49-51] and in experimental animals,[52,53] is the toxic/septic shock; all other imaginable influences cause either hyperthermia r no effect on body temperature. Another common feature between MS and toxic shock is the presence of nausea, a sensation that is a part of defense against intoxication. Experiments using rats have shown that hypothermia and cold-seeking behavior during toxic shock is not only defensive but actually critical for survival.[54,55] The adaptive value of these reactions is in reducing tissue demands for oxygen that is critical for survival during intoxication.[56] Thus, one could speculate that if both nausea and hypothermia develop during MS, they might reflect an activation of the same defense mechanism. Given this assumption, the question now is: defense against what during motion sickness? An intriguing proposal has been made by Ossenkopp who was the first to observe motion-induced hypothermia.[14] The essence of Treisman's and Ossekopp's ideas is complemented with few of our thoughts and is presented in the following paragraph.

Our bodies possess several lines of defense against intoxication.[57] The first level is distant – unpleasant smell or unappealing appearance of the food would prevent us from its ingestion. The second level is represented by gustatory receptors – we spit out anything with nasty taste. Level 3 comprises the protective mechanisms in the stomach which is vomiting (including 5-HT3 receptors on the afferent vagal ending that, when activated, cause nausea and vomiting). If a neurotoxin passes this line of defense, it may then activate nausea/vomiting and hypothermia by acting in certain "sensor" brain areas, e.g., area postrema[58] – a fourth line of defense. Taking into account Reason and Brands' sensory mismatch theory of motion sickness,[59] Treisman made 2 suggestions: i) that another "sensor" area comprises "the systems involved in controlling movement, including eye movements, and determining the location of the body in space" that are "almost continually in action and highly susceptible to even a minor degree of disruption; they constitute an ideal warning system for detecting early central effects of neurotoxins, where these have not activated more basic levels of defense;" and ii) that stimuli that elicit motion sickness, just by accident, activate this last level of defense.[60] In other words, vestibular and/or visual stimuli capable to provoke motion sickness do so by accidentally activating integrated response primarily designed to attenuate effects of toxins (by reducing metabolism) and to prevent their ingestion in the future (by inducing nausea that is extremely efficient in producing aversive conditioning). Speaking about nausea, Treisman concludes: "If this suggestion is correct, motion sickness is an adaptive response evoked by an inappropriate stimulus"[60]; we believe this statement is equally applicable to MS-induced hypothermia.

Table 1. Objective signs of motion sickness in humans and motion-induced effects in rodents. It is obvious that most of changes that occur in humans fit into a "thermoregulatory cluster" (dashed line). The table also identifies potential directions for further validation of the rodent model of motion sickness

Humans	Rodents
Facial pallor	N/A
Sweating	N/A
Fall in body T	Fall in body T
Skin vasodilation	Skin vasodilation
Reduced thermogenesis	?
Preference for cooler environment	?
Gastric dysrhythmia	?
Rise in plasma vasopressin	No

Benefits of thermoregulation-related indices as measures of MS-induced nausea

The evidence for the close link between nausea and thermoregulation has one important practical implication. Currently, assessing nausea in preclinical research is a major technical problem. Measuring retching/vomiting in species that possess emetic reflex has limited value for studying nausea; most commonly used laboratory animals – rats and mice – do not possess vomiting reflex. Common symptoms in humans – sweating and facial pallor – cannot be measured in rodents. There is no real-time physiological biomarker of nausea in animals. The only established and relatively specific biochemical marker of nausea in humans, elevated plasma vasopressin[61,62] have not been confirmed in rats.[63] Consequently, rodent studies of nausea have to rely on indirect indices, often with poor temporal resolution and specificity (locomotor activity, food consumption) or, in addition, with limited face validity (pica – an unconventional consumption of kaolin.[64] Conditioned taste aversion is a powerful method, but the measure is not real-time and could not be used for assessing unconditioned responses. There is thus no real-time physiological biomarker of nausea. Future work in both humans and animals is required to determine whether assessment of thermoregulation-related indices (core and surface temperature, skin blood flow, sweating and basic metabolic rate) during vestibularly- or visually-induced motion sickness could represent the first real-time unconditioned markers of nausea. If so, this will open new opportunities for revealing the neural substrate of nausea and for the search for efficient anti-nausea substances.

Conclusions and Perspectives

This review presents ample evidence to suggest that disturbances in thermoregulation play a central role in the pathophysiology of motion sickness. Looking from this angle at so-called "cold

sweating" during nausea, one would immediately realize that it is a part of integrated physiological response aimed to reduce body temperature. With this in mind, one would realize that most of objective signs of MS are related to thermoregulation (**Table 1**). Providing that nausea is a part of natural defense against poisoning, body cooling following the detection of a toxin possibly represents an evolutionary beneficial "defensive hypothermia." This is supported by the fact that such "defensive hypothermia" occurs during toxic shock, in both humans and in animal models. It may be that provocative visual or vestibular stimuli accidentally trigger this coordinated defensive response. Testing this hypothesis may be a productive way to advance our knowledge about the neural substrate of nausea.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

References

1. Stern R, Koch K, Andrews P. Nausea. New York: Oxford University Press; 2011
2. Golding JF, Kerguelen M. A comparison of the nauseogenic potential of low-frequency vertical versus horizontal linear oscillation. Aviat Space Environ Med 1992; 63:491-497; PMID:1520219
3. Kennedy R, Lane N, Berbaum K, MG L. Simulator sickness questionnaire: An enhanced method for quantifying simulator sickness. Int J Aviat Psy 1993; 3:203-220; http://dx.doi.org/10.1207/s15327108ijap0303_3.
4. Hesse W. Ein beitrag zur seekrankheit Arch d Helik 1874; 15:130-142
5. Ogata K. ST. On the causes of diurnal body temperature rhythm in man, with reference to observations during voyage. Jpn J Physiol 1963; 13:84-96; PMID:13939555; http://dx.doi.org/10.2170/jjphysiol.13.84
6. Hemingway A. Cold sweating in motion sickness. Am J Physiol 1944; 141:172-175.
7. Crampton G. Studies of motion sickness: Xvii, physiologicd changes accompanying sickness in man. J Appl Physiol 1955; 7:501-507; PMID:14367236
8. Mekjavic IB, Tipton MJ, Gennser M, Eiken O. Motion sickness potentiates core cooling during immersion in humans. J Physiol 2001; 535:619-623; PMID:11533150; http://dx.doi.org/10.1111/j.1469-7793.2001.00619.x
9. Cheung B, Hofer K. Coriolis-induced cutaneous blood flow increase in the forearm and calf. Brain Res Bull 2001; 54:609-618; PMID:11403987; http://dx.doi.org/10.1016/S0361-9230(01)00463-4
10. Nobel G, Eiken O, Tribukait A, Kolegard R, Mekjavic IB. Motion sickness increases the risk of accidental hypothermia. Eur J Appl Physiol 2006; 98:48-55; PMID:16847677; http://dx.doi.org/10.1007/s00421-006-0217-6
11. Nobel G, Tribukait A, Mekjavic IB, Eiken O. Histaminergic and cholinergic neuron systems in the impairment of human thermoregulation during motion sickness. Brain Res Bull 2010; 82:193-200; PMID:20394809; http://dx.doi.org/10.1016/j.brainresbull.2010.04.004
12. Cheung B, Nakashima AM, Hofer KD. Various anti-motion sickness drugs and core body temperature changes. Aviat Space Environ Med 2011; 82:409-415; PMID:21485398; http://dx.doi.org/10.3357/ASEM.2903.2011
13. Nobel G, Tribukait A, Mekjavic IB, Eiken O. Effects of motion sickness on thermoregulatory responses in a thermoneutral air environment. Eur J Appl Physiol 2012; 112:1717-1723; PMID:21892631; http://dx.doi.org/10.1007/s00421-011-2142-6
14. Ossenkopp KP, Rabi YJ, Eckel LA, Hargreaves EL. Reductions in body temperature and spontaneous activity in rats exposed to horizontal rotation: Abolition following chemical labyrinthectomy. Physiol Behav 1994; 56:319-324; PMID:7938244; http://dx.doi.org/10.1016/0031-9384(94)90201-1
15. Ngampramuan S, Cerri M, Del Veccio F, Corrigan JJ, Kamphee A, Dragic AS, Rudd JA, Romanovky AA, Nalivaiko E. Thermoregulatory correlates of nausea in rats and musk shrews. Oncotarget 2014; 5:1565-75; PMID:24728971
16. Del Vecchio F, Nalivaiko E, Cerri M, Luppi M, Amici R. Provocative motion causes fall in brain temperature and affects sleep in rats. Exp Brain Res 2014; 232:2591-9; PMID:24658633; http://dx.doi.org/10.1007/s00221-014-3899-8
17. Machado-Moreira CA, Barry RJ, Vosselman MJ, Ruest RM, Taylor NA. Temporal and thermal variations in site-specific thermoregulatory sudomotor thresholds: Precursor versus discharged sweat production. Psychophysiology 2014 (in press); PMID:25048252; http://dx.doi.org/10.1111/psyp.12292
18. Golding JF. Phasic skin conductance activity and motion sickness. Aviat Space Environ Med 1992; 63:165-171; PMID:1567315
19. McClure JA, Fregly AR, Molina E, Graybiel A. Response from arousal and thermal sweat areas during motion sickness. Aerosp Med 1972; 43:176-179; PMID:4537005
20. Golding JF, Stott JR. Comparison of the effects of a selective muscarinic receptor antagonist and hyoscine (scopolamine) on motion sickness, skin conductance and heart rate. Br J Clin Pharmacol 1997; 43:633-637; PMID:9205824; http://dx.doi.org/10.1046/j.1365-2125.1997.00606.x
21. Wan H, Hu S, Wang J. Correlation of phasic and tonic skin-conductance responses with severity of motion sickness induced by viewing an optokinetic rotating drum. Percept Mot Skills 2003; 97:1051-1057; PMID:15002846; http://dx.doi.org/10.2466/pms.2003.97.3f.1051
22. Himi N, Koga T, Nakamura E, KObashi M, Yamane M, Tsujioka K. Differences in autonomic responses between subjects with and without nausea while watching an irregularly oscillating video. Auton Neurosci 2004; 116:46-53; PMID:15556837; http://dx.doi.org/10.1016/j.autneu.2004.08.008
23. Cowings PS, Suter S, Toscano WB, Kamiya J, Naifeh K. General autonomic components of motion sickness. Psychophysiology 1986; 23:542-551; PMID:3809361; http://dx.doi.org/10.1111/j.1469-8986.1986.tb00671.x
24. Isu N, Koo J, Takahashi N. Changes of skin potential level and of skin resistance level corresponding to lasting motion discomfort. Aviat Space Environ Med 1987; 58:136-142; PMID:3827789
25. Warwick-Evans LA, Church RE, Hancock C, Jochim D, Morris PH, Ward F. Electrodermal activity as an index of motion sickness. Aviat Space Environ Med 1987; 58:417-423; PMID:3593144
26. Parker DM. A psychophysiological test for motion-sickness susceptibility. J Gen Psychol 1971; 85:87-92; PMID:5099582; http://dx.doi.org/10.1080/00221309.1971.9920656
27. Hu S, Grant WF, Stern RM, Koch KL. Motion sickness severity and physiological correlates during repeated exposures to a rotating optokinetic drum. Aviat Space Environ Med 1991; 62:308-314; PMID:2031631
28. Hu S, McChesney KA, Player KA, Bahl AM, Buchanan JB, Scozzafava JE. Systematic investigation of physiological correlates of motion sickness induced by viewing an optokinetic rotating drum. Aviat Space Environ Med 1999; 70:759-765; PMID:10447048
29. LaCount LT, Barbieri R, Park K, Kim J, Brown EN, Kuo B, Napadow V. Static and dynamic autonomic response with increasing nausea perception. Aviat Space Environ Med 2011; 82:424-433; PMID:21485400; http://dx.doi.org/10.3357/ASEM.2932.2011
30. Guo CT, So RHY, Kwok K, Cheung R. Fects of foveal retinal slip on visually induced motion sickness under controlled of eye motions. Proceedings of the 56th Annual Meeting of the Human Factors and Ergonomics Society, Oct., Boston, MA, USA; 2012; 22-26.
31. Kim K, Rosenthal MZ, Zielinski DJ, Brady R. Effects of virtual environment platforms on emotional responses. Comp Methods Progr Biomed 2014; 113:882-893; http://dx.doi.org/10.1016/j.cmpb.2013.12.024
32. Min YK, Chung SC, You JH, Yi JH, Lee B, Tack GR, Chun JH, Park MS, Min BC. Young adult drivers' sensitivity to changes in speed and driving mode in a simple vehicle simulator. Percep Motor Skills 2006; 103:197-209.
33. Min BC, Chung SC, Min YK, Sakamoto K. Psychophysiological evaluation of simulator sickness evoked by a graphic simulator. Applied ergonomics 2004; 35:549-556; PMID:15374762; http://dx.doi.org/10.1016/j.apergo.2004.06.002
34. Cui J, Iwase S, Mano T, Kitazawa H. Responses of sympathetic outflow to skin during caloric stimulation in humans. Am J Physiol 1999; 276:R738-744; PMID:10070134
35. Sunahara F, Johnson W, Taylor N. Vesibular stimulation and forearm blood flow. Can J Physiol Pharmavol 1964; 62:199-207; http://dx.doi.org/10.1139/y64-023
36. Sinha R. Coriolis reactions on respiration and blood-flow changes. Aerosp Med 1968; 837-844; PMID:5302437
37. Foubert J, Vaessen G. Nausea: The neglected symptom? Eur J Oncol Nurs 2005; 9:21-32; PMID:15774338; http://dx.doi.org/10.1016/j.ejon.2004.03.006
38. Di Maio M, Bria E, Banna GL, Puglisi F, Garassino MC, Lorusso D, Perrone F. Prevention of chemotherapy-induced nausea and vomiting and the role of neurokinin 1 inhibitors: From guidelines to clinical practice in solid tumors. Anticancer Drugs 2013; 24:99-111; PMID:23165435; http://dx.doi.org/10.1097/CAD.0b013e328359d7ba
39. Smith JE, Paton JF, Andrews PL. An arterially perfused decerebrate preparation of suncus murinus (house musk shrew) for the study of emesis and swallowing. Exp Physiol 2002; 87:563-574; PMID:12481931; http://dx.doi.org/10.1113/eph8702424
40. Napadow V, Sheehan JD, Kim J, Lacount LT, Park K, Kaptchuk TJ, Rosen BR, Kuo B. The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex 2013; 23:806-813; PMID:22473843; http://dx.doi.org/10.1093/cercor/bhs073
41. Billig I, Yates BJ, Rinaman L. Plasma hormone levels and central c-fos expression in ferrets after systemic

administration of cholecystokinin. Am J Physiol. Regul, Integr Comp Physiol 2001; 281:R1243-1255; PMID:11557633
42. De Jonghe BC, Horn CC. Chemotherapy agent cisplatin induces 48-h fos expression in the brain of a vomiting species, the house musk shrew (suncus murinus). Am J Physiol. Regul, Integr Comp Physiol 2009; 296:R902-911; PMID:19225146
43. Horn CC. Brain fos expression induced by the chemotherapy agent cisplatin in the rat is partially dependent on an intact abdominal vagus. Auton Neurosci 2009; 148:76-82; PMID:19362521; http://dx.doi.org/10.1016/j.autneu.2009.03.008
44. Balaban CD, Ogburn SW, Warshafsky SG, Ahmed A, Yates BJ. Identification of neural networks that contribute to motion sickness through principal components analysis of fos labeling induced by galvanic vestibular stimulation. PloS one 2014; 9:e86730; PMID:24466215; http://dx.doi.org/10.1371/journal.pone.0086730
45. Romanovsky AA. Thermoregulation: Some concepts have changed. Functional architecture of the thermoregulatory system. American journal of physiology. Regul, Integr Comp Physiol 2007; 292:R37-46; http://dx.doi.org/10.1152/ajpregu.00668.2006
46. McAllen RM, Tanaka M, Ootsuka Y, McKinley MJ. Multiple thermoregulatory effectors with independent central controls. Eur J Appl Physiol 2010; 109:27-33; PMID:19949811; http://dx.doi.org/10.1007/s00421-009-1295-z
47. Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci (Landmark Ed) 2011; 16:74-104; PMID:21196160
48. Lewisohn L. The sacred meditation of islam: Sama' in the persian sufi tradition. Br J Ethnomeditation 1997; 6:1-33.
49. Clemmer TP, Fisher CJ, Jr., Bone RC, Slotman GJ, Metz CA, Thomas FO. Hypothermia in the sepsis syndrome and clinical outcome. The methylprednisolone severe sepsis study group. Critical Care Med 1992; 20:1395-1401.
50. Laupland KB, Davies HD, Church DL, Louie TJ, Dool JS, Zygun DA, Doig CJ. Bloodstream infection-associated sepsis and septic shock in critically ill adults: A population-based study. Infection 2004; 32:59-64; PMID:15057568; http://dx.doi.org/10.1007/s15010-004-3064-6
51. Marik PE, Zaloga GP. Hypothermia and cytokines in septic shock. Norasept ii study investigators. North american study of the safety and efficacy of murine monoclonal antibody to tumor necrosis factor for the treatment of septic shock. Intensive Care Med 2000; 26:716-721; PMID:10945388; http://dx.doi.org/10.1007/s001340051237
52. Romanovsky AA, Shido O, Sakurada S, Sugimoto N, Nagasaka T. Endotoxin shock: Thermoregulatory mechanisms. Am J Physiol 1996; 270:R693-703; PMID:8967396
53. Almeida MC, Steiner AA, Branco LG, Romanovsky AA. Neural substrate of cold-seeking behavior in endotoxin shock. PloS One 2006; 1:e1; PMID:17183631; http://dx.doi.org/10.1371/journal.pone.0000001
54. Liu E, Lewis K, Al-Saffar H, Krall CM, Singh A, Kulchitsky VA, Corrigan JJ, Simons CT, Petersen SR, Musteata FM, et al. Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and escherichia coli-induced systemic inflammation. Am J Physiol. Regul, Integr Comp Physiol 2012; 302:R1372-1383; PMID:22513748
55. Romanovsky AA, Shido O, Sakurada S, Sugimoto N, Nagasaka T. Endotoxin shock-associated hypothermia. How and why does it occur? Ann N Y Acad Sci 1997; 813:733-737; PMID:9100963; http://dx.doi.org/10.1111/j.1749-6632.1997.tb51775.x
56. Romanovsky AA, Szekely M. Fever and hypothermia: Two adaptive thermoregulatory responses to systemic inflammation. Med Hypotheses 1998; 50:219-226; PMID:9578327; http://dx.doi.org/10.1016/S0306-9877(98)90022-6
57. Davis CJ. Emesis research: A concise history of the critical concepts and experiments. In: Reynolds DJM, Andrews PLR, Davis CJ., ed. Serotonin and the scientific basis of anti-emetic therapy. Oxford Clinical Communications; 1995; 9-25.
58. Hornby PJ. Central neurocircuitry associated with emesis. Am J Med 2001; 111 Suppl 8A:106S-112S; PMID:11749934; http://dx.doi.org/10.1016/S0002-9343(01)00849-X
59. Reason J, Brand J. Motion sickness. London: Academic Press; 1975.
60. Treisman M. Motion sickness: An evolutionary hypothesis. Science 1977; 197:493-495; PMID:301659; http://dx.doi.org/10.1126/science.301659
61. Fisher RD, Rentschler RE, Nelson JC, Godfrey TE, Wilbur DW. Elevation of plasma antidiuretic hormones (adh) associated with chemotherapy-induced emesis in man. Cancer Treat Rep 1982; 66:25-29; PMID:7053263
62. Rowe JW, Shelton RL, Helderman JH, Vestal RE, Robertson GL. Influence of the emetic reflex on vasopressin release in man. Kidney Int 1979; 16:729-735; PMID:548611; http://dx.doi.org/10.1038/ki.1979.189
63. Verbalis JG, McHale CM, Gardiner TW, Stricker EM. Oxytocin and vasopressin secretion in response to stimuli producing learned taste aversions in rats. Behav Neurosci 1986; 100:466-475; PMID:3017374; http://dx.doi.org/10.1037/0735-7044.100.4.466
64. McCaffrey RJ. Appropriateness of kaolin consumption as an index of motion sickness in the rat. Physiol Behav 1985; 35:151-156; PMID:4070378; http://dx.doi.org/10.1016/0031-9384(85)90329-4