Clinical and physiological characteristics of cybersickness

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I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

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I hereby certify that some parts of the work embodied in this thesis have been done in collaboration with other researchers. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

Alireza Mazloumi Gavgani

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List of Abbreviations

ANOVA	Analysis of variance
BA	Brodmann area
BP	Blood pressure
CBF	Cerebral blood flow
CI	Confidence interval
DAP	Diastolic arterial pressure
ECG	Electrocardiography
HR	Heart rate
HRV	Heart rate variability
HMD	Head mounted device
HbO2	Oxygenated haemoglobin
MCA	Middle cerebral artery
MSSQ	Motion sickness susceptibility questioner
MSAQ	Motion sickness assessment questioner
MS	Motion sickness
NIRS	Near Infrared spectroscopy
PCA	Posterior cerebral artery
RMSSD	Square root of the mean squared differences
RMS	Root Mean Square
RC	Rotating chair
SDRR	Standard deviation of R-R intervals
SAP	Systolic arterial pressure
SCL	Skin conductance level
SEM	Standard error of the mean

TCD	Transcranial Doppler
VIMS	Visually induced motion sickness
VR	Virtual reality

Abstract

In the last two decades there have been substantial advances in the development of virtual reality (VR) technology for various applications such as entertainment, education and training. However, limited knowledge is available about the side effects of this technology including cybersickness - a form of motion sickness that is caused by immersion in VR. My present study is aimed at providing an insight into cybersickness in order to better understand the physiological characteristics of this averse phenomenon. In this study, a total of 79 healthy volunteers (41 females, 38 males) were exposed to cybersickness provoking VR content (virtual ride on a rollercoaster using Oculus Rift head-mounted display) in four independent research experiments.

In the first experiment (described in Chapter 2), we investigated the symptom profile of cybersickness and explored if desensitization can occur with repetitive exposure. We found that gastrointestinal symptoms such as nausea are the most common symptoms associated with cybersickness followed by other - central, peripheral and sopite-like symptoms. We found that these symptoms can last over 3 hours after exposure. Our results clearly demonstrate that repetitive exposure to virtual environments can result in habituation to cybersickness. Our findings demonstrate that forehead sweating increases significantly with increasing nausea and therefore, forehead sweating can be a reliable biomarker for cybersickness in general and nausea in particular.

In the second experiment (described in Chapter 3), we examined the effects of visual content on the intensity of cybersickness symptoms. We found that changes in the direction of visual flow of the same VR content has a significant effect on the severity of sickness such that moving forward in a virtual environment is more provocative than moving backward.

In the third experiment (described in Chapter 4), two different imaging modalities were used to analyse brain hemodynamic during cybersickness. We found that cybersickness is associated with variations in brain activity (region-specific increases and decreases) in a complex network in numerous cortical regions related to the cognitive, evaluative and sensory discriminative aspects of this syndrome. Our results demonstrate that overall sensitivity to cybersickness was significantly higher in females than males.

In the fourth experiment (described in Chapter 5), we compared the subjective symptoms and physiological effects of cybersickness induced by virtual reality and “classic” motion sickness triggered by vestibular stimulation (Coriolis cross-coupling). We found that despite fundamental differences in provoking stimuli, cybersickness and motion sickness are clinically identical. We conclude that cybersickness is a complex syndrome, and that its symptoms and physiological effects are far beyond the common gastrointestinal symptoms.

My work represents detailed characterisation of symptoms and physiological changes that accompany cybersickness. The major impact of my work is, firstly, in the identification of a selective and sensitive biomarker that will allow detection, monitoring and quantification of cybersickness in future studies. Secondly, my finding of similarity between cybersickness and “classical” motion sickness opens opportunity for translational work, namely developing of a simple test for assessing motion sickness susceptibility, and a novel approach for motion sickness desensitization.

Chapter 1: Introduction

1.1 Motion sickness: definition

Motion sickness is a common illness affecting the general population. This illness comprises the aversive sensation of nausea as well as a number of autonomic and hormonal changes (cold sweating, facial pallor, rise in plasma vasopressin) (1). These symptoms have been described in many studies investigating this complex syndrome (2-4).

Motion sickness is a condition that has been known for thousands of years. Although the great deal of research has been conducted into why and how motion sickness affects people, there are still many questions that have yet to be answered. This introductory chapter provides an overview of the history of motion sickness research (section 1.2), the theories that have been put forth about why and how motion sickness occurs (section 1.3, 1.7-1.8), and the different types of motion sickness that have so far been identified (section 1.4-1.6) including cybersickness, which is the focus of this dissertation.

1.2 History

Sea travel was a significant development in the history of mankind. This resulted in the discovery of new continents, new trade routes and a surplus of new ideas and commerce that continues to reshape the world up until present. Professional sailors were in high demand; however, not everyone was suited. Early reports of motion sickness can be dated back to the first sailing vessels. A study by Huppert et al. traced back the ancient literature discussing seasickness or “plague at sea,” to before 300 BC (5). The ancient Greeks and Romans understood that a person’s psychological state could affect the intensity of seasickness, and experienced sailors were resistant to motion sickness. Hippocrates (460-377 B.C.) wrote: "Sailing on the sea proves that motion disorders the body" (6). The Chinese medical classics distinguished several forms of travel sickness, and each form was given its own written character (7). Early Chinese medical books observed that children were especially susceptible to motion sickness. These books also defined other types of motion sickness induced by traveling (e.g. cart-sickness and sedan chair or litter-sickness) (7, 8).

Huppert et al. notes that many ancient sources emphasize the impact of motion sickness on the outcomes of major historical events, especially battles like the Battle of the Redcliff which led

to the defeat of the Spanish Fleet by the English in 1588 (8), and motion sickness triggered by riding on camels during Napoleon's campaign in Egypt 1798/1799. Thus, since ancient times motion sickness was recognized as a physiological response to unadapted body motions during passive transportation as well as a "plague at sea".

Eastern and Western theories of motion sickness were not perfectly aligned. The Greek "pathophysiology" of seasickness was founded on the work of Empedokles and Aristoteles who believes that the stomach was the main cause of seasickness. Chinese medicine however attributed forms of motion sickness to certain bodily substances and the life force, *Qi* (5). Some traditional therapies were also closely investigated by the ancient scientists. While Western books recommended therapeutic measures like specific diets, fasting, medicinal plants, a mixture of wine and wormwood, Eastern literature produced even more uncommon methods, such as swallowing white sand-syrup or drinking the urine of young boys (5).

More common therapies such as ingestion of ginger before travel has also been linked to ancient therapies (9-11). Despite the fact that ginger has long been used in many cultures as a medication to prevent motion sickness, the mechanism of its action is still unknown. Interestingly, in relatively recent years some scientists have conducted studies to test whether this ancient therapy indeed works. Some studies have shown that ginger can be effective in reducing motion sickness (10, 12). A double blind study by Lien et al. (10) used ginger to reduce motion sickness symptoms in thirteen volunteers who had histories of motion sickness. These volunteers underwent circular vection[1] with and without ginger treatment. Pre-treatment with ginger (1,000 and 2,000 mg) was found to reduce nausea, tachygastria, and plasma vasopressin as well as reducing the recovery time and prolonged the latency before nausea onset. Traditionally, ginger has been used in other remedies as well for similar purposes - for instance to reduce vomiting and nausea during pregnancy (9) or in order to stimulate digestion (11). One of the studies validating ginger's effectiveness in motion sickness was performed on board a vessel at sea and involved 80 naval cadets who were unfamiliar with sailing; this study found that ginger reduced the tendency to vomit and the incidence of cold sweats compared to a placebo (13). Further controlled clinical studies are essential to investigate the effectiveness of ginger for motion sickness.

[1] Vection is the sensation of movement of the body in space caused by visual stimulation

Although motion sickness has been known for centuries, it's only more recently that the general public has been exposed to it. With the development of the transportation industry and the availability of personal vehicles, sailing yachts and commercial airliners the incidence of motion sickness experienced by the ordinary public has increased. The incidence of motion sickness is so common in everyday travel that some transportation vehicles such as small commercial flights and passenger cruise ships provide emesis bags. Approximately 30% of ocean liner passengers (14) and 40% of flight trainees in the Royal Air Force (15) are reported to have experienced MS. Even the most advanced space vehicles are piloted by crews that report experiencing motion sickness at a rate of nearly 60% (16) .

Throughout history, motion sickness has remained a challenge for human eagerness to travel either physically or virtually. As Reason and Brand (6) write "*whenever we relinquish our intended status as self-propelled animals and step aboard some vehicle or device that transports us passively we incur the risk of motion sickness. This wretched and debilitating condition has always been intimately linked with man's technological efforts to improve and extend his natural powers of locomotion*".

1.3. Etiology of motion sickness

Despite the fact that there is no comprehensive explanation for the etiology of motion sickness, there are few theories that partially explain this syndrome. A common pattern of all motion or visual provocations which induce motion sickness is a repetitive linear or angular acceleration. Most researchers agree that the vestibular organ plays a critical role in the pathogenesis of motion sickness and previous studies have concluded that people with vestibular disorders such as bilateral labyrinthine deficiency are not sensitive to motion.

First described by Irwin (17) and later confirmed by James (18), researchers have repeatedly demonstrated that people with bilateral middle ear damage are not susceptible to seasickness under conditions that characteristically produced MS in normal populations (19). What follows is a brief summary of the causal theories that have been put forth by researchers as they attempted to explain motion sickness and its mechanisms. After a discussion of the causes I provide an account of the different types of motion sickness that have been identified by researchers. It must be emphasized that the theories that will be discussed here are not necessarily exclusive or exhaustive, in other words elements of each theory may be true at least for certain situations, and these theories can interact with each other.

1.3.1. Sensory conflict theory

The theory that currently dominates the medical and academic fields' understanding of motion sickness suggests that the condition develops when conflicting signals are received from the senses that provide spatial orientation - the vestibular system, the eyes and the non-vestibular proprioceptors. This theory was first proposed by Reason and Brand (6) and later updated (with mathematical modelling) by Oman (20). Sensory conflict can originate within a single sensory system such as the vestibular system canal-otolith conflict, or between two or more sensory systems such as visual-vestibular conflict (6), or between the expected sensory input and the actual input (e.g. a lag between head rotation and expected visual input while using virtual reality devices). However, vision on its own is not essential for motion sickness since blind people are susceptible to MS (21). Despite some reports of symptoms of motion sickness in individuals with bilateral vestibular loss (BVL) (22), in general subjects with bilateral vestibular deficit are believed to be immune not only to motion-induced MS but also to visually-induced MS (22, 23). In this case, visual stimuli work as triggers for MS but the vestibular system is considered essential for its development. Reason and Brand describe this condition as follows: "*this conflict between the present evidence of our special senses and that held in store from our previous experience is considered to be the crucial factor in triggering motion sickness*" p.134 (6). They further argue that this mismatch or difference generates neuronal signals whose magnitude is proportionate to the amount of conflict and the severity of symptoms. As exposure to provocative stimuli continues, the current sensory inputs gradually update earlier sensory memories and expectations based on these memories, and this results in reduction of the magnitude of the conflict and consequently the intensity of the symptoms; the authors named this process as "sensory rearrangement".

1.3.2. Postural instability theory

Riccio and Stoffregen's theory of MS suggests that lack of postural control (postural instability) is responsible for motion sickness (24). The authors state that "…*animals become sick in situations in which they do not possess (or have not yet learned) strategies that are effective for the maintenance of postural stability*". This theory concludes that motion sickness increases as a result of external motion interference with the naturally arising body sway activity that occurs at the frequency range of 0.1– 0.3 Hz. This theory suggests that maintaining

postural position by sitting, holding on to something or laying down can diminish MS symptoms.

Considering this approach, Riccio and Stoffregen's theory emphasizes that postural instability is not only a consequence of motion sickness, but also its cause. Consequently, individuals who already exhibit poor postural control are believed to be more susceptible to motion sickness even before any form of stimulus is presented (25).
It must be noted that although motion sickness due to postural instability can extended to sickness caused by motion, however it is hard to imagine how VIMS can be explained by this theory especially when the individual is sitting or lying in bed with minimal movement

1.3.3. Fluid shift theory

Fluid shift theory suggests that space sickness which is a form of motion sickness is a consequence of shifts in cranial body fluids subsequent to loss of hydrostatic pressure gradients in the lower body during microgravity (26-28). The cranial fluid shift results in puffiness in the face, and is thought to increase the intracranial pressure, the cerebrospinal-fluid pressure or the inner ear fluid pressures, thereby altering the response properties of the vestibular receptors and consequently resulting in space motion sickness. Simanonok et al. (25) used 9 pre-flight variables related to fluid, electrolyte, and cardiovascular status to classify 64 first-time astronauts according to their space sickness incidence (Sick or Not sick) with a success rate of 80%. These 9 variables are serum uric acid, red blood cell count, serum phosphate, urine osmolality, serum thyroxine, sitting systolic blood pressure, calculated blood volume, serum chloride, and environmental temperature at the launch site. This study supports its findings with pre-flight and post-flight echocardiographic comparisons of heart volumes in 19 shuttle astronauts and concludes that "*exaggerated physiologic adaptation to fluid shifts is associated with space sickness*" (26).

It is without doubt that cranial fluid shift can create substantial physiological side effects ultimately contributing to the aforementioned averse sensations, however, some studies have discarded fluid shift being the dominating cause of space sickness (29) due to mismatching time course of sickness and weightlessness. Obviously, more research studies are essential to further understand the side effects of zero-gravity and its potential effect in the development of MS.

1.3.4. Toxic theory

Heat loss through skin is a major thermoregulatory mechanism in mammals. There are several animal studies performed showing that rats and shrews experience hypothermia during rotation around vertical axis (30, 31). Many studies have shown that hypothermia occurs during Motion Sickness (32-34). When the arterio-venous anastomoses are dilated it allows a significant volume of warm blood to get in closer contact to the ambient and therefore despite heat. However, in humans this process is rather controversial, although some studies have reported transient vasodilation in the forearm and calf during MS provocation (35) many studies have described vasoconstriction during MS (36) (32). However, what is quite clear is that motion sickness is linked with social behaviours and physiological responses that aims to reduce the core body temperature by any means, such as preference for cooler environment commonly reported by individuals and sweating to reduce body temperature (37). As described by Eugene et al. (38) this coordinated response is less likely to be an evolutionary reaction since until the early sea voyages humans were rarely exposed to any motion that could have caused sickness. Furthermore, When hyperthermia induced by MS is compared with other physiological responses that trigger body temperature drop it is obvious that symptoms such as nausea, vomiting, stomach awareness, desire not to eat, cold sweat and physiological responses are very similar (38). Eugene et al concludes that any stimuli including completely visual that would trigger motion sickness do so by unintentionally initiating integrated response designed to reduce effects of toxins and to prevent any further ingestion in the future by bringing nausea.

In this study we used forehead skin conductance level as a biomarker for the theromoregulatory response caused by motion sickness provocative stimuli. T2–T3 segments of the spinal cord and the superior cervical ganglion controls the cutaneous vasomotor activity and sweating in the face (39). Two types of vasomotor control are known to be present in human skin. (1) Areas of skin such as the ear, lip and nose in which vasomotor control is primarily mediated by variations in vasoconstrictor tone; and (2) areas of skin such as the scalp, forehead, chin, submandibular area in which vasomotor control is principally mediated by active vasodilatation (40)`(41). In other words cutaneous vasodilation in certain regions of the face may coincide with vasoconstriction in other regions. This to some extent can explain the simultaneous facial pallor and sweating common symptoms of MS.

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This theory attempts to explain some of the symptoms during motion sickness. This theory is based on the idea of evolutionary survival mechanism which erroneously interprets visual-vestibular mismatch as a sign of intoxication because many neurotoxins cause such mismatch. Accordingly, this defence mechanism triggers protective reaction directed towards removal of a toxin from the gut by cooling down the body (sweating) and aversive sensation of nausea to condition an individual against future ingestion of a toxic substance (42). Nausea and eventually vomiting can be considered as adaptive reaction to eject any remaining toxic substances.

1.4. Symptomatology of MS

The cardinal signs of motion sickness are nausea, dizziness, facial pallor, cold sweating and in extreme cases vomiting. The associated physiological reactions to motion sickness include yawning, hypoventilation, flatulence and drowsiness (2, 43-45). The toxic theory is a convincing theory that to some extent explains some symptoms experienced in motion sickness. However, this theory fails to clarify other symptoms such as dizziness and disorientation which are commonly reported during motion sickness (43, 46).

Another physiological response which scientists have attempted to explain using the "toxic" theory is loss of body heat during MS (37). There are several well-documented studies on hypothermia caused by motion sickness (30, 32, 37) which are also backed by some animal studies (30). Losing heat through the glabrous skin is one of the major thermoregulatory mechanisms in mammals who have developed arterio-venous anastomoses. Dilation of these anastomoses permits a significant volume of warm blood to get in close proximity with the ambient air to dissipate heat in sub-thermoneutral environment and reduce body temperature (30, 37). One of the early reports of decrease in body temperature during motion sickness is by Ogata (47) who documented that his body temperature was lower on the days of rough sea when he experienced nausea compared to normal days of voyage. Since this early reporting there has been many studies confirming the effect of MS on thermoregulation (32). Sweating is another well-known MS symptom, which has been reported in numerous studies regardless of how MS was triggered (2, 37, 43-45, 48-52). Obviously, some scientists see sweating as another indicator that during motion sickness a coordinated decrease in core body temperature is occurring. Some of these studies have documented that sweating intensity increased with increasing nausea (33, 43, 53). Therefore, the toxic theory can be a reasonable explanation which shows that the increase in sweating trigged by nausea as another mechanism to reduce

body temperature in a misinterpreted response of intoxication (37). Nalivaiko et al. writes "*…MS triggers coordinated cognitive, behavioural and physiological changes that act synergistically to cool down the body*" and "*…Providing that nausea is a part of natural defence 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*".

1.5. Brain and motion sickness

Although a link between neural metabolism and perfusion in the brain has been of interest to many researchers (54-56), there is limited knowledge available on cerebral blood flow (CBF) and brain hemodynamic during MS. One of the reasons for lack of research in this area is the inherent limitation of movement causing motion artefacts and other major technical restrictions with current imaging methods. In recent years some studies have used visual MS provocation methods to conduct research on CBF during MS. Changes in cortical activity during motion sickness and nausea have been reported using functional magnetic source imaging (57), electroencephalography (58) and fMRI (59). These studies have shown that several brain areas are involved during Visually Induced Motion Sickness (VIMS), including vestibular nuclei, the hypothalamus, parts of the cerebellum, the area postrema, the medulla oblongata (nucleus tractus solitaries), and parts of the reticular formation (60, 61). In Chapter 4 of this study we will investigate CBF and hemodynamic of the brain during visually induced motion sickness.

1.5.1 Autonomic nervous system and motion sickness

Autonomic nervous system (ANS) plays an indispensable role in the development of motion sickness and symptoms such as nausea (62). Both divisions of the ANS, sympathetic and parasympathetic, are involved in the physiological responses to nauseogenic stimuli. A meta-analysis of publications investigating the effects of ANS parasympathetic nervous tone (PNS) showed that there is significant withdrawal in the PNS tone in subjects whom experience VIMS when compared to resistant subjects (63). An animal study on Suncus murinus (Asian house shrew) which unlike rats do have the emesis reflex suggest that the predominance of parasympathetic nervous activity is relevant to the enhancement of motion stimuli-induced

emetic response, whereas the predominance of sympathetic nervous system (SNS) activity suppresses motion stimuli-induced emetic response.

It appears that the event of vomiting has a very different ANS profile to the general motion sickness syndrome. A study by Cowings et al. reported that during the development of motion sickness, there is general SNS activation and PNS withdrawal (64). We know that the mean of successive differences in heart beats correlates to PNS activity and SCL correlates to SNS activity. The connection between motion sickness and ANS was confirmed by Hu et al. (65), who reported negative correlation between the mean of the differences between successive heart beats and positive correlation with skin conductance with increasing motion sickness. In other words, when motion sickness increased SCL increased and HRV decreased.

This contradiction of the ANS profile during motion sickness and vomiting further explains the complexity and dynamic nature of autonomic nervous system variations during motion sickness.

1.6. New subtypes of motion sickness

Motion sickness is initiated by particular types of motion and is induced through passive movement in vehicles, generated by unexperienced body accelerations, to which the person has been not desensitized, or by an internal sensory conflict. While throughout history motion sickness has been associated with physical movement such as a moving vessel, car, or a rollercoaster, with the introduction of new technologies and modern gadgets a new form of this aversive sensation has emerged, specifically, visually induced motion sickness and space sickness. Despite sharing symptomatology with traditional motion sickness, these new forms of MS are different from the traditional MS considering the provocative stimuli.

1.6.1. Space sickness

Space sickness or space adaptation syndrome is another form of MS, which includes similar symptoms to traditional motion sickness. More than 60% of astronauts have experienced space sickness (66). In the Shuttle programme almost 80% of U.S astronauts reported some level of space sickness (67). Space sickness appears within the first few hours in the microgravity environment, but is not seen at launch, when the astronaut is exposed to linear acceleration. This syndrome is repeatedly triggered by active head movement, which does not produce terrestrial motion sickness. Two hypotheses have been proposed to explain space motion

sickness: the fluid shift hypothesis and the sensory conflict hypothesis. In both of them, weightlessness is thought to be the main cause of vestibular stimulation in space.

1.6.2. Visually Induced Motion Sickness (VIMS)

Possibly the first case of visually induced motion sickness was reported in 1894 (68). An oversized swing that was located in the centre of a normal size room. This swing could accommodate 15 people at a time. This was not an ordinary swing since instead of the swing moving back and forward, the room was designed in a way that it will move and eventually spin, creating an illusion of spinning. Nausea, dizziness and disorientation was reported by many whom tried the swing.

Sensory conflict theory has been described as the main cause of VIMS. Obviously, this conflict rises from the visual sensory input. Apart from the sensory conflict theory, eye movements have also been described as one potential root mechanism for VIMS (69). According to the eye movement theory, optokinetic nystagmus (OKN) evoked by moving visual patterns can lead to VIMS.

1.6.3. Simulator sickness

Simulator sickness is another form of motion sickness that is experienced by pilots who undertake flight simulator training. The symptoms of simulator sickness is very similar to classic motion sickness, however these symptoms are induced in simulated situations and can be triggered without real physical motion. Common symptoms reported by the trainees experiencing this condition are disorientation, fatigue, nausea and vomiting. Although these symptoms may not be life-threatening, this general discomfort can decrease the efficiency of the simulator training and therefore result in reduced simulator application.

Simulators are used in the aviation industry due to their numerous advantages compared to live aircraft training, for instance emergency measures and safety can be taught and practiced, the training is not interrupted by unwanted weather conditions, they are cost effective, and also there are special training options available with simulation that do not exist in live aircraft training (70) (71). Simulators map real movements to virtual images displayed on screens.

These images may not resemble the movement expected by the user. Therefore, it is believed that this condition is caused by mismatch between the actual movement and the movement displayed on the digital screen.

1.6.4. Cybersickness

Cybersickness is a form of motion sickness which is provoked by exposure to virtual reality. This sensation is thought to be caused by the feeling of movement in a virtual environment while being stationary (see review (25)). Although cybersickness and simulator sickness is believed to share similar symptomatology, some studies have suggested that cybersickness can produce more severe symptoms compared to simulator sickness (72); however, our findings described in chapter 5 contradict these previously reported results. There is an undisputable relationship between cybersickness, simulator sickness and motion sickness considering the underlying physiological causes and types of symptoms (73). Although these symptoms may vary from person to person, some of the most common symptoms related to cybersickness – nausea, dizziness and disorientation – remain the same.

Modern virtual reality (VR) devices are mainly represented by head-mounted displays (HMD) that provide computer-simulated virtual environments for its users (74). Although VR devices have been around for decades (75), due to their high cost and limited application there has been little research conducted in understanding these tools. Recent technological advances resulted in the entry of VR devices into the consumer market. VR devices such as Computer Automatic Virtual Environment (CAVE) or Nintendo play stations allow users to experience virtual environments. More recently, Facebook had acquired Oculus VR (a developer of the Oculus Rift, the first consumer HMD) and is focusing on developing new virtual applications. The Facebook CEO Mark Zuckerberg stated in March 2014 that *"…this is just the start. After games, we're going to make Oculus a platform for many other experiences. Imagine enjoying a court side seat at a game, studying in a classroom of students and teachers all over the world or consulting with a doctor face-to-face – just by putting on goggles in your home…"*– With the increasing trend in the application of VR in everyday life, cybersickness is the main complication for widespread adoption and commercial expansion of technologies linked with virtual environments, especially in fields like education and training.

Whether or not individuals are affected by cybersickness is highly dependent on the scale of provocation and on individual sensitivity. However, cybersickness is relatively common, and majority of people do feel some level of sickness during the VR experience. A study on cybersickness symptoms (76) discovered that 80% of subjects experienced symptoms of cybersickness in the first 10 minutes of their VR exposure. Some of these symptoms lasted for more than 24 hours. Without doubt, cybersickness is a negative factor affecting the application and widespread usability of VR environments. However, safety issues represent another concern affecting the everyday application of VR technology. Therefore, in order to extend the application of this innovative tool, further research should be performed. The research can provide essential information in order to identify susceptible individuals from one hand and to identify the most provocative element of VR from the other hand.

1.7. Motion sickness susceptibility

There are many factors which contribute to individual susceptibility to motion sickness. Individuals from different ethnic backgrounds may have different sensitivity to motion. Other factors such as sex and age are also considered as contributing factors (77). Previous reports show that Females are more susceptible to visually induced motion sickness (74). Kolasinski reported that children between 4-12 years are more prone to MS compared to adults, and susceptibility to MS provocations in childhood correlated with the susceptibility in adulthood period (78).

A variety of motion sickness questionnaires have been used to assess MS susceptibility. They provide information gathered about the individual's motion sickness historical experiences resulting from different types of provocative motion (i.e. bus rides, car, etc.). Reason and Brand's Motion Sickness Susceptibility Questionnaire (MSSQ) is the most common and validated approach. This questionnaire was later updated by Golding (2). This questionnaire collects individual's childhood and adulthood travel experiences and their relation to any nausea or vomiting. A score is calculated for each individual which indicates how sensitive one is to MS: the larger the score, the higher is the sensitivity. Similar questionaries have been used in experimental conditions to assess participants' symptoms (73).

1.8. Measuring Motion Sickness

While the underlying mechanisms that cause MS are still not completely understood, there are many studies using subjective and objective measures in an attempt to quantify it.

1.8.1. Subjective approaches

One of the earliest questionnaires used as a subjective measure to assess motion sickness was the Pensacola Motion Sickness Questionnaire (79). This questionnaire provided pre-experiment and post-experiment questions to define symptoms experienced by participants during the exposure. This questionnaire was constantly modified throughout the years. Later other similar questionnaires were developed for assessing simulator sickness in the military (80). Some other subjective scales have been used to generally rate nausea (81).

A common questionnaire applied to assess 16 most common symptoms is the Motion Sickness Assessment Questionnaire (MSAQ) was designed by Gianaros et al. (3). This psychometric instrument is used to measure the symptoms which are classified into four different clusters - gastrointestinal, central, peripheral, and sopite. Table 1 shows all questions related to each category (3).

Table 1. List of categorized questions in MSAQ.

Gastrointestinal		Central		Peripheral		Sopite	
Q1	I felt sick to my stomach	**Q5**	I felt faint-like	**Q10**	I felt sweaty	**Q13**	I felt annoyed/irritated
Q2	I felt queasy	**Q6**	I felt lightheaded	**Q11**	I felt clammy /cold sweat	**Q14**	I felt drowsy
Q3	I felt nauseated	**Q7**	I felt disoriented	**Q12**	I felt hot/warm	**Q15**	I felt tired/fatigued
Q4	I felt as if I may vomit	**Q8**	I felt dizzy			**Q16**	I felt uneasy
		Q9	I felt like I was spinning				

Because the MSAQ (3) is one of the most commonly used multivariate questionnaires for recording motion sickness symptoms, we have also adopted it into our own study hoping to see

a correlation with the objective results. Simulator sickness questionnaire (SSQ) is another common questioner that has been used to assess motion sickness predominantly in simulators, this questionnaire also contains oculomotor symptoms such as eyestrain and blurred vison(73).

Although self-reporting can provide insight into a variety of symptoms experienced with cybersickness, different ratings can be obtained from individuals depending on their perception of severity. This fact introduces difficulties in analysing the results quantitatively.

1.8.2. Objective Measures of Motion Sickness

When compared to self-reporting questionnaires, measuring physiological parameters could be difficult to record and analyse due to the disturbances caused by movements; however, these objective parameters can provide essential details of physiological response during motion sickness which subjective ratings do not provide.

There are numerous studies focusing on objective parameters in order to evaluate pathogenesis of the general form of motion sickness. They used heart rate, respiratory rate, changes in gastric myoelectric activity and in cardiac vagal tone, sweating, disturbances in thermoregulation (30, 61, 82-84) (32, 48, 51, 85). Electroencephalography (EEG) and plasma vasopressin have also been used to investigate motion sickness (1, 38, 82, 83). Kim et al. (86) used eye blink rate, electrooculogram (EOG) and photoplethysmogram (PPG) as well as 14 other parameter in a study investigating cybersickness. Ohyama et al. (87) used heart rate variability during immersion in virtual reality. Among several biological variables, sweating rate is demonstrated to be one of the most consistent, and there are studies that reported its correlation with in nausea during motion sickness (48, 50, 52). The earliest study where increase in sweating was observed during MS provocation, was conducted by Hemingway (88) 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. Consequently, rise in tonic SCL was established. Since then many other research studies have used this parameter to investigate motion sickness (43, 45, 48, 50-52).

Although level of sweating has been reported as a reliable indicator of MS, the location of the electrodes is also important. Sweating in some regions of the body such as fingers or on the palms of a hand can be triggered by other factors such as excitement and emotional arousal as well as MS (89). There is some evidence that sweating in the forehead could be more closely

related to subjective rating of nausea (48); this is one of the primary hypotheses we are going to test.

1.9. Motion Sickness Desensitization

Physiological responses to MS have been used in the literature to determine whether desensitization to motion sickness occurs. Repetitive provocations can make individuals less susceptible to MS (90), which is why a habituation protocol is used in the military student pilots and in aircrew to overcome motion sickness. It has been demonstrated that repeated exposure to gradually more provocative stimulation can eventually result in reduction or complete disappearance of the symptoms. Cheung and Hofer (90) reported evidence of desensitization within four days to three different provocative stimulations. This study reports that there is also evidence of habituation to a less provocative stimulation using an initial stronger vestibular habituation stimulation (90). Habituation to motion sickness was reported to retain completely for a period of month and partially for one year after desensitization to optokinetic stimuli was achieved in a study on 34 subjects suffering from motion sickness (91).

In Australia, MS desensitisation program is routinely conducted at AVMED (RAAF Aviation Medicine Institute in Edinburgh, SA). The protocol comprises 2 weeks of repetitive (5 times per day) session of cross-Coriolis coupling (rotation in a flight simulator, with head tilts; Fig. 1). This program is thus lengthy, expensive and requires participants to travel to AVMED.

Fig. 1. Flight simulator used for motion sickness desensetization program at AVMED

1.10. Thesis structure

It is now well appreciated that in the near future virtual environments will dominate in many aspects of our lives - from entertainment to education, training and trade. Despite the fact that this technology has a significant positive impact on our lives, the drawbacks should be studied in detail in order to prevent undesirable side effects. The main objective of the current study is to better understand the concept of cybersickness in the context of its physiological side effects and biomarkers and attempt to shed light on areas that have not been explored in previous investigations.

In the second chapter we investigated the development and progress of common cybersickness symptoms. Also, in this chapter we aimed to investigate the effect of repetitive exposure to provocative stimuli on symptoms and the concept of desensitization to cybersickness.

The third chapter aims to describe how the direction of visual flow in VR affects intensity of MS and post-exposure symptoms. In this study, physiological parameters as well as subjective reporting are recorded to monitor changes caused by visual flow in opposite directions.

In Chapter 4 the hemodynamic of the brain during cybersickness is investigated. This study aims to discover the changes in the brain before and after cybersickness with novel approaches. Two state-of-the-art imaging modalities are used to measure blood perfusion and neural activation when participants are experiencing cybersickness induced by virtual environment. To the best our knowledge these techniques have not been used so far to investigate brain hemodynamic during cybersickness.

In chapter 5 we investigate and compare cybersickness with classical motion sickness induced by physical motion. The aim of this experiment is to discover any differences and similarities between classical motion sickness and cybersickness. Subjective and objective data are compared in both conditions.

I will conclude this dissertation by providing brief review of findings and conclusions in previous chapters.

Chapters 2-5 represent four of our recently published research articles, as indicated in the corresponding footnotes. I was the first author in all of these articles.

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Chapter 2: Profiling subjective symptoms and autonomic changes associated with cybersickness

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A/Prof Eugene Nalivaiko

Abstract

Our aim was to expand knowledge of cybersickness – a subtype of motion sickness provoked by immersion into a moving computer-generated virtual reality. Fourteen healthy subjects experienced a 15-min rollercoaster ride presented via a head-mounted display (Oculus Rift), for 3 consecutive days. Heart rate, respiration, finger and forehead skin conductance were measured during the experiment; this was complemented by a subjective nausea rating during the ride and by Motion Sickness Assessment Questionnaire before, immediately after and then 1, 2 and 3h post-ride. Physiological measurements were analysed in three dimensions: ride time, association with subjective nausea rating and experimental day. Forehead, and to a lesser extent finger phasic skin conductance activity showed a correlation with the reported nausea ratings, while alteration in other measured parameters were mostly related to autonomic arousal during the virtual ride onset. A significant habituation was observed in subjective symptom scores and in the duration of tolerated provocation. The latter increased from 7.0±1.3 min on the first day to 12.0±2.5 min on the third day ($p<0.05$); this was associated with a reduced slope of nausea rise from 1.3±0.3 units/min on the first to 0.7±0.1 units/min on the third day ($p<0.01$). Furthermore, habituation with repetitive exposure was also determined in the total symptom score post-ride: it fell from 1.6±0.1 on the first day to 1.2±0.1 on the third ($p<0.001$). We conclude that phasic changes of skin conductance on the forehead could be used to objectively quantify nausea; and that repetitive exposure to provocative VR content results in habituation.
Key words: Cybersickness, motion sickness, nausea, habituation, skin conductance.

2.1. Introduction

It is currently well accepted that motion sickness (MS, or kinetosis) develops when conflicting signals are received from the spatial orientation senses - vestibular, visual and proprioceptive. Such sensory conflict can be initiated within a single sensory system such as canal-otolith interaction during Coriolis cross-coupling, or between two or more sensory systems such as visual/vestibular/proprioceptive interaction when on a boat in rough seas (1). MS could be provoked by a broad variety of causes, and it is according to these causes and also according to the predominant sensory influence that MS has been historically classified as sea-, air- or carsickness; simulator sickness; space sickness; and visually-induced motion sickness. The key role of the vestibular system in the pathogenesis of MS is evident from the fact that subjects with bilateral vestibular deficit are immune not only to vestibular but also to visual provocations (2-4).

Cybersickness refers to MS induced by the immersion of stationary users in moving scenes using computer-generated virtual reality (VR), especially with the assistance of more immersive interfaces such as VR head-mounted displays. Although such VR devices have been around for decades (5, 6), due to their high cost and limited application there has been little research conducted in understanding the biological impact of these devices. With the increasing trend in the application of VR and computer games in everyday life, it becomes evident that cybersickness is the main obstacle in broad adoption and commercial expansion of VR technology, especially in fields like education and training. There are numerous factors of VR technology that could be responsible for these alterations; generally they could be classified into two categories: hardware-dependent (e.g. a lag between head move and visual field move, monitor flicker, disaccord between vergence and accommodation) and content-dependent (e.g. vigorous linear and/or angular accelerations) (6). Information regarding potential effects of cybersickness on human physiology is limited, and expanding this area was our primary aim for this work

The most common and known symptoms of MS are cold sweating, nausea and vomiting, and facial pallor (1, 3); previous studies however revealed that the list of MS symptoms is substantially longer. It is now accepted in the field that all MS is a multidimensional syndrome, and that all its symptoms could be split into four clusters: gastrointestinal (stomach awareness, nausea, vomiting); central (fainting, light headiness, disorientation, dizziness, sensation of spinning); peripheral (sweating, feeling hot) and sopite (annoyance, drowsiness, tiredness, uneasiness) (7). A common established psychometric tool for their assessment is Motion Sickness Assessment Questionnaire (MSAQ) (7). It appears that there are some differences in symptom profile between the subtypes of MS: for example, Kennedy and colleagues reported that some symptoms of simulator sickness are less severe and less common compared to “classic” MS (8). To the best of our knowledge, symptom profiling of cybersickness has never been performed, and this was one of our aims; this was complemented by an attempt to establish objective biological markers that could be used for assessing and monitoring nausea during cybersickness. Here, we suggested that similar to vestibular provocations, the most sensitive measure would be phasic changes of skin conductance on the forehead (9, 10). Lastly, we aimed to determine whether repetitive exposure to the provocative VR content would result in habituation (i.e. reduction of objective signs and subjective symptoms of cybersickness following repetitive exposure to VR) like it occurs during repetitive vestibular provocations

(eg. (11, 12)). To this end, we exposed our volunteers for 3 consecutive days to a 15-min virtual ride on a roller coaster using the Oculus Rift, a common consumer VR product; we Concurrently recorded ECG, respiratory rate and phasic and tonic changes in skin conductance in fingers and on the forehead, and assessed both immediate and delayed symptoms of cybersickness.

2.2. Methods

2.2.1 Participants and general experimental outline

The study was conducted in 14 healthy volunteers (average age 29 ± 6.1 range 18-37 years old) of both genders (8 female and 6 males), with the approval of the Human Research Ethics Committee of Newcastle University. In this study each participant was asked to undergo a simulated roller coaster ride for three consecutive days. On the first day, on arrival to the lab (air conditioned room kept at 21–22°C), subjects rested for 10 minutes, signed an informed consent form and completed the and revised motion sickness susceptibility questionnaire (MSSQ) (13); this was complemented by a question regarding previous experience with VR. After fitting the head-mounted virtual display (Oculus Rift DK1, Oculus VR, USA), we obtained a 5-min baseline recording of heart rate, respiration rate, finger skin conductance and forehead skin conductance. During this period a static stereoscopic neutral image was displayed on the screen. Subsequently, the rollercoaster simulation ride (Helix, Archivision, NL) was activated and lasted for a maximum of 15 minutes. However, the participants were able to terminate the ride whenever they felt uncomfortable to proceed. During the ride subjects were asked to rate their level of motion sickness every minute on the scale from zero (no effect) to 10 (severe MS - just about to vomit). After the ride, subjects completed the Motion Sickness Assessment Questionnaire (MSAQ) (7); this assessment was also repeated 1, 2 and 3h post-ride to rate the regress of the symptoms. The symptoms were categorized into four clusters: gastrointestinal (nausea, feeling sick in the stomach, feeling queasy, about to vomit) central (faint-like, light headiness, disoriented, dizzy and spinning), peripheral (sweaty, hot, clammy, cold sweat, temperature discomfort) and sopite (annoyed, drowsy, tired, uneasy). When answering each question of the MSAQ, the participant assigns a value from a range of 1 “not at all” to 9 “severe”. These ratings are then summed for each group of related questions and used in a formula for each subscale, where Rating = (Sum of each subclass symptom rating)/[(number of the questions related to the corresponding subclass) × 9]. The overall MSAQ motion sickness score is calculated as: Score = (Sum of all items / [(Number of all

questions) × 9]. On each of the experimental days, subjects also rated the delayed symptoms 1 h, 2 h and 3 h after the termination of virtual ride.

2.2.2. Data collection and analysis

ECG and respiration was measured using 3-lead electrodes and respiratory belt respectively. The finger and forehead skin conductance levels (SCL) were measured using constant voltage UFI Model 2701 BioDerm Skin Conductance Meter (UFI, Morro Bay, USA). For both SCL locations, we used 8 mm diameter silver/silver chloride electrodes filled with conductive gel (UFI, Morro Bay, USA). The finger electrodes were positioned on the palmar surface of middle phalanxes of the index and the middle fingers of non-dominant hand. The forehead electrodes were placed on the right and left sides of the forehead 1 cm bellow the hairline, at about the lateral corners of the eyes. All the sensors were connected to PowerLab-8s data acquisition system and a computer running Chart 8.0 (ADInstruments, Sydney, Australia). Sampling rate was 1 kHz for ECG and 100 Hz for respiratory and skin conductance signals. Heart rate (HR) and respiratory rate were computed online using R-R ECG intervals and the peaks of respiratory signal, respectively. To compute the phasic component of the skin conductance signal we applied a high pass filter with a cut-off frequency of 0.05Hz (9, 10). Amplitude Root Mean Square (RMS) and the frequency of SCL transients in the phasic component was calculated using LabChart software.

For the purpose of statistical analysis, all signals were averaged at 1-min intervals. Statistical analyses were performed using Prism v.6.1 (GraphPad, USA). One-way ANOVAs for repeated measures were performed to determine the effects of time on nausea rating, the effect of repetitive provocation on the ride duration and the effect of repetitive exposure on the slope of nausea rating vs. time relationship. The slope was determined by a linear fitting procedure according to the formula (Nausea rating = m x Time + c), where m is a slope. Spearman's correlation was used to assess relations between the MSSQ score and ride duration. We performed two types of analysis of physiological parameters: i) dependence of measured variables on riding time; and ii) dependence of measured variables on nausea rating; we also determined whether habituation of MS symptoms occurred during the second and the third provocation. As all participants terminated their ride at different times, we could not perform overall averaging of their data traces for the first type of analysis; instead, similar to (9), we selected for comparison three points: baseline (before the ride), the first minute of the ride, and

the last minute of the ride (i.e. when the nausea level was the highest). For the second type of analysis, data were split into "no nausea" (rating 0), "light nausea" (rating 1-3), "moderate nausea" (rating 4-6) and "strong nausea" (rating >6) bins. Two-way 3 x 3 factorial design ANOVAs for repeated measures were then applied, with the two factors being the recording time (baseline, first and last min of the ride) and the day (1^{st}, 2^{nd}, 3^{rd}) for the first type of analysis; and nausea rating and the day for the second type. Follow-up analyses were conducted using Student's t-tests, with a Bonferroni correction for multiple comparisons for each outcome variable separately. Data are presented as means ± standard error of the mean (SEM). Statistical significance was set at $p<0.05$.

2.3. Results

2.3.1. Effects of virtual ride on nausea levels

All participants reported vection and some level of nausea during the ride. Only one of the participants managed to complete the 15 minutes ride in all three days and the rest terminated the ride before completing due to nausea. Average nausea rating for first day was zero at baseline, 0.6±0.3 for 1^{st} min of the ride and 5.3±0.4 for the last min of the ride (Fig. 1A); there was no difference in the maximum nausea between the three experimental days. While there was no change in mean ride time on the second day, compared to the first day, there was a substantial (66%) and significant (F (2, 22) = 4.787, p=0.0188, η^2=0.12) increase in ride duration on the third day (Fig. 1C). There was also a significant reduction in the "nausea rating *vs.* time" slope on the 3^{rd} day compared to the first two days (1.3±0.26, 1.3±0.20 and 0.7±0.1 units/min, respectively; F (2, 24) = 6.4, p=0.0059, η^2=0.13, Fig. 1D).

None of the subjects had previous experience of VR gaming. Participants differed substantially in their MSSQ score; it ranged from 4 to 48 mean (17±15). MSSQ scores were significantly and negatively correlated with the ride duration on the first day (r = -0.72, p = 0.018; Fig. 1B). While the trend for this inverse relationship was present in the second and the third day, it was not significant (Table 1). There was no correlation between the MSSQ score and maximal nausea rating reached during the ride on any of three days.

Table 1. Changes of total score for symptoms of cybersickness evaluated before, immediately after and 1, 2 and 3 h after the termination of virtual ride, on three consecutive days.

	Before ride	Just after	1 H	2 H	3 H
Day 1	0.03±0.01	0.38±0.03****	0.21±0.05****####	0.15±0.05****####	0.11±0.03*#### XXX
Day 2	0.03±0.01	0.33±0.03****Y	0.17±0.03****####	0.09±0.03#### XX	0.08±0.02#### XXX
Day 3	0.03±0.01	0.29±0.04****YYY	0.15±0.05****####Y	0.08±0.032 #### XY	0.06±0.03#### XX

*Data are presented as Mean ± S.E.M. Significance: *, *** and **** - p<0.05, p<0.001 and p<0.0001 respectively compared to "Before ride"; #### - p<0.0001 compared to the "Just after ride"; X, XX and XXX – p<0.05, p<0.01 and p<0.001, respectively, compared to "Hour 1"; Y and YYY – p<0.05 and p<0.001, respectively, compared to Day 1.*

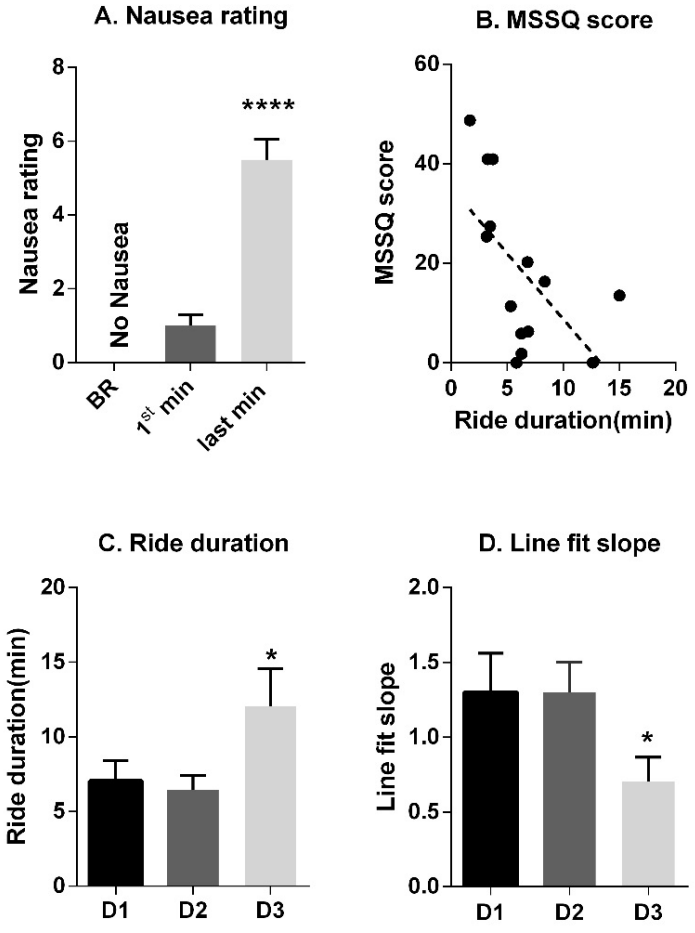

Fig. 1. A. Average nausea rating during the experiment on Day 1. BR – before ride; **** - *p<0.0001* compared to BR. B. Relationship between MSSQ score and tolerated ride duration on Day 1. Dashed line shows result of linear regression. C. Tolerated ride duration on each day of experiment; D1, D2 and D3 – 1st, 2nd and 3rd day, respectively. C. Average slope of linear regression for individual's nausea rating on each day of experiment. * - *p<0.05 compared to D1.*

2.3.2. Immediate and delayed subjective symptoms induced by virtual ride.

Two-way ANOVA revealed significant effects of both "time of ride" (F (4, 44) = 24.78, p<0.0001, and "day" (F (2, 22) = 4.18, p=0.03) factors. Before the ride, mean MSAQ symptoms score was 0.03±0.01; the score increased significantly immediately after the ride (F (4, 44) = 24.78, p<0.0001), and gradually declined starting from 1 h post-ride (Fig. 4 A and Table 1). Post-hoc tests indicated highly significant differences between "Before the ride" and both "Just after" and "1h post-ride" for all three days; differences for later time points (2 and 3h post-ride) were significant only during Day 1. Post-hoc tests for the "day" factor revealed significant differences between Day 1 and both Day 2 and Day 3 for the "Just after the ride" and "2h post-ride" time point, and between Day 1 and Day 3 for the "1h post-ride" time point (Fig. 2A, Table 1). Distribution of MS symptoms after the ride on the 1st day according to the four clusters are shown in Fig. 2B. This rank order (GI > Sopite > Central > Peripheral) remained similar on the two following days of experiment. Of interest, occasionally our subjects reported that some symptoms (loss of appetite, feeling sick in the stomach and fatigue) persisted for up to 10 hours after the completion of an experiment.

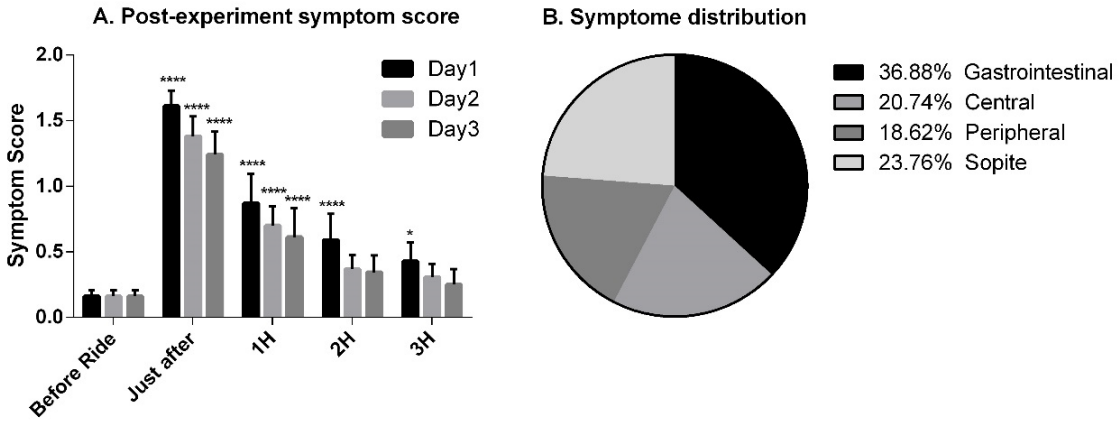

Fig. 2. Subjective symptoms of cybersickness. A - Temporal changes of total symptom score during and after the virtual ride on three experimental days; ** and **** - p<0.05 and p<0.0001, respectively, compared to "Before ride"*. B - Distribution of symptom according to four clusters on Day 1.

The temporal course of each symptom cluster during each of the three experimental days is presented in Fig. 3. Overall, the within-day trend for individual clusters was similar to the total score, in that repetitive provocations resulted in shorter (<2h) persistence of all symptoms. The major difference here was found with the "just after the ride" time point: while the intensity of

sopite and central scores remained stable across the three days (Fig. 3A & 3C), there was significant habituation in the peripheral cluster, and a trend for such habituation in the GI cluster (Fig. 3B & 3D).

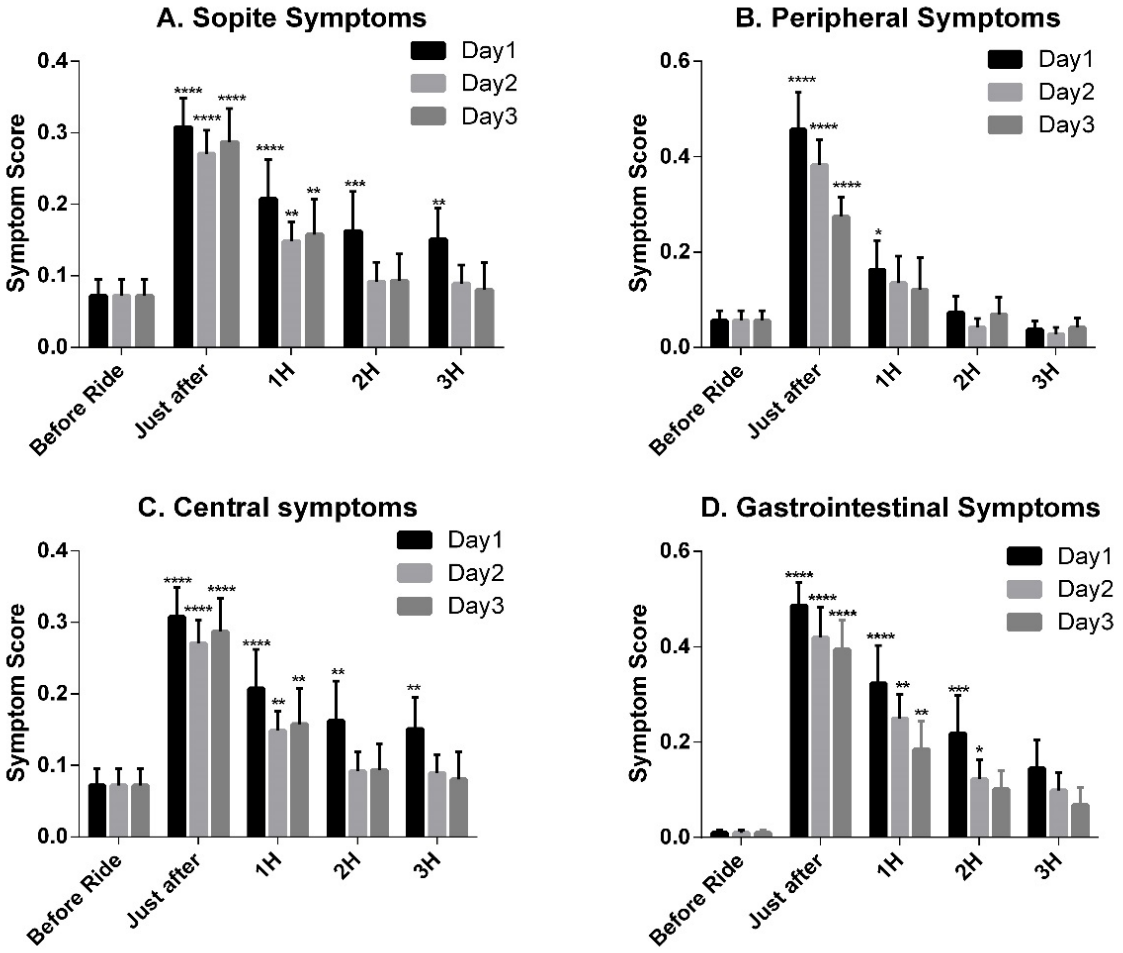

Fig. 3. Temporal changes of symptoms score for each cluster during and after the virtual ride on three experimental days. A – Sopite; B – Peripheral; C – Central; D – Gastrointestinal. *Significance: *, **, *** and **** - p<0.05, p<0.01, p<0.001 and p<0.0001, respectively.*

2.3.3. Relations between virtual ride time and cardiorespiratory changes

An example of physiological recordings and nausea ratings obtained in one subject during the simulated ride is shown in Fig. 4. There was no difference in baseline HR between days (Table 2). On the first day, ride onset was associated with a small but significant tachycardia (+9.3 ± 2.1 bpm) ($F(2, 26) = 7.418$, $p=0.0028$, $\eta^2= 0.08$) that gradually diminished but was still present at the end of the ride (Figs. 4, 5A and Table 2). This initial tachycardic response was still

present on the Day 2 ($F(2, 26) = 4.702$, $p=0.0181$) but became non-significant on the Day 3 (+3.5 ± 1.5 and +4.2 ± 1.8 bpm, respectively ;($F(2, 24) = 2.36$, $p=.1162$, $\eta^2=0.03$).

There was no difference in baseline respiratory rate between days (Table 2). During simulated ride, respiratory rate generally followed the trend observed in HR. On the 1st day, ride onset was associated with a small but significant tachypnoea (+2.2 ± 0.6 cpm) that gradually dissipated towards the end of the ride (Figs. 4, 5B and Table 2). This initial tachypnoeic response remained unchanged on the 2nd day (+2.8 ± 0.7, $F(2, 26) = 5.222$, $p=0.0195$) and became non-significant on the 3rd day, ($F(2, 24) = 1.676$, $p=0.2082$, $\eta^2=0.04$).

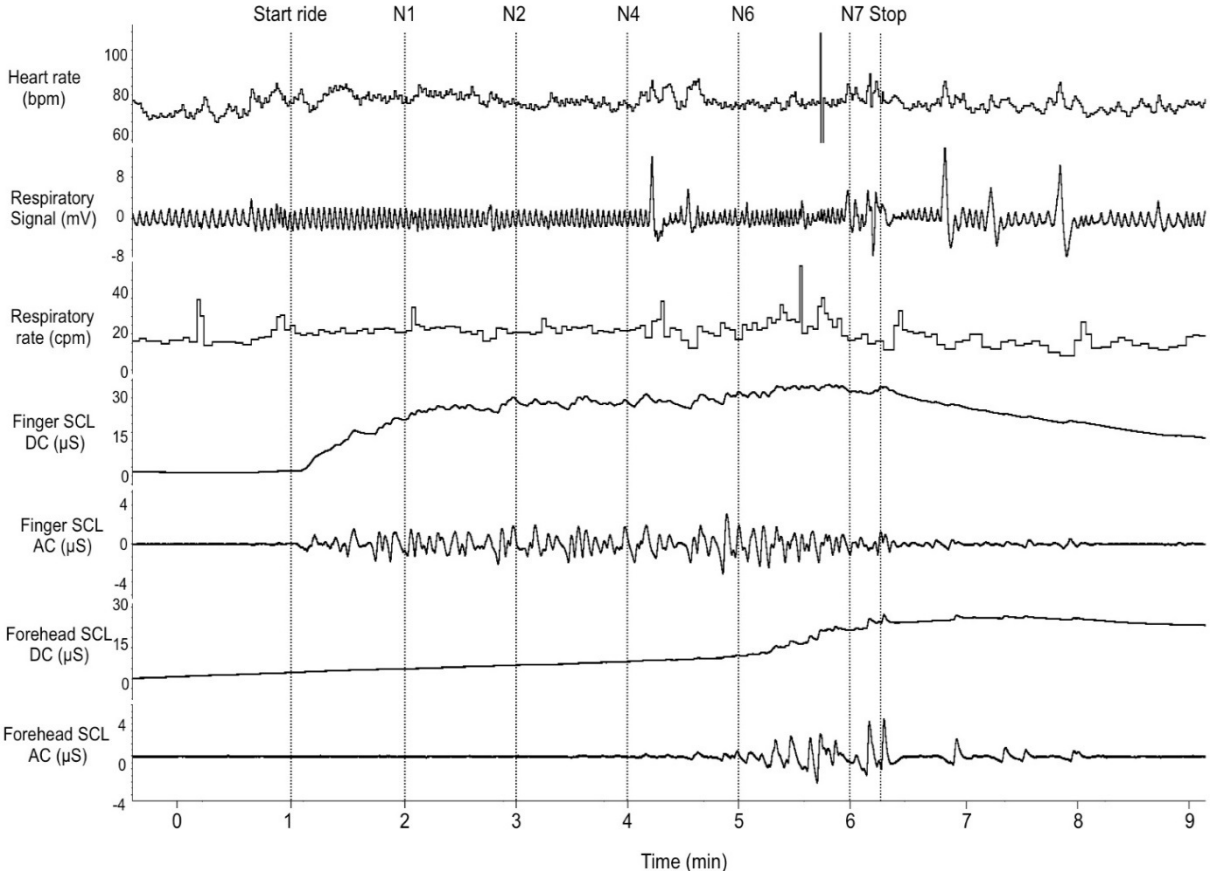

Fig. 4. An example of physiological recordings obtained in one subject during the simulated ride. Traces (from top to bottom): heart rate, respiratory signal, respiratory rate, singer skin conductance level (SCL) tonic, finger SCL phasic, forehead SCL tonic, forehead SCL phasic. The first and the last vertical lines indicate the start and the end of virtual ride, respectively. Numbers above other lines indicate nausea level experienced by the subjects.

2.3.4. Relations between virtual ride time and skin conductance levels

There was no difference in the baseline finger tonic SCL on the three experimental days. An example of tonic and phasic skin conductance recording is shown in Fig. 4. Ride onset causes rapid (within several seconds) increase in finger SCL. On the 1st min of the ride on the 1st day it raised by +9.2±2.5μS ($F(2, 26) = 19.01$, $p<0.0001$, $\eta^2=0.392$) indicating increasing sweating in the finger; this response further increased towards the end of the ride (Fig. 4 and 5C). The initial (1st minute of the ride) increase in tonic finger SCL showed a decreasing trend on the 2nd and 3rd day (+5.5 ± 1.3 and 4.4 ± 1.4 μS, respectively; Table 2). Phasic finger SCL activity was quite variable at baseline: in some subjects it was virtually absent whereas in others it was well expressed. If the activity was absent, there was a very obvious appearance of phasic SCL events within several seconds following ride onset (Fig. 4); in those with ongoing baseline activity, changes were less obvious. Overall, there were no significant differences in the frequency ($F(2, 26) = 1.819$, $p=.18$, $\eta^2=0.05$) of the phasic events or in RMS ($F(2, 26) = 1.381$, $p=.26$, $\eta^2=0.03$) values of the SCL signal between baseline and the ride, and no overall difference between the three experimental days (Figs. 5D, 5E and Table 2).

An example of tonic and phasic forehead skin conductance recordings are shown in Fig. 4. There was no difference in the tonic forehead SCL signal at baseline on the three experimental days, and no overall effect of provocations. There was virtually no phasic SCL activity at the forehead during baseline (Figs. 4, 5G and 5H), with no between-days difference (Table 2). In the majority (12/14) of participants, phasic events gradually appeared during simulated ride; this occurred at different times, and their appearance was clearly associated with nausea ratings (see next section). There were substantial and highly significant differences in the phasic events frequency ($F(2, 26) = 4.73$, $p=0.0185$, $\eta^2=0.07$) and in RMS levels ($F(2, 26) = 7.888$, $p=0.0023$, $\eta^2=0.27$), of the forehead SCL signal between the baseline and the last minute of the ride (Figs. 5G and 5H); these differences persisted during the 2nd and 3rd days (Table 2).

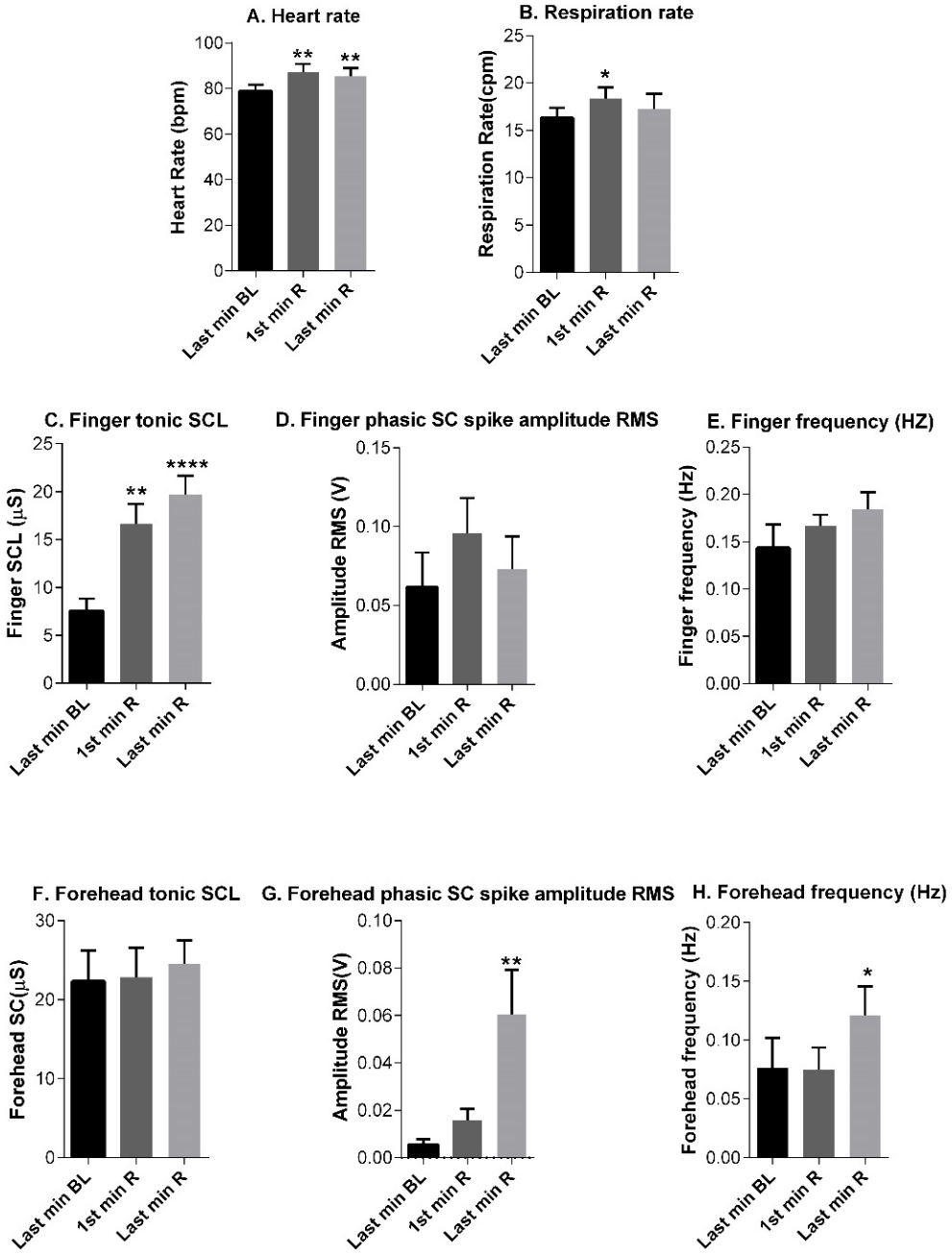

Fig. 5. Changes in recorded physiological parameters during experimental session on the first day. On each graph, 3 bars represent data values for the last minute of baseline period and for the first and the last minutes of simulated ride. A - Heart rate; B - Respiratory rate; C - Finger tonic (DC) skin conductance level; D - Finger phasic (AC) skin conductance spike amplitude RMS; E - Finger phasic skin conductance spike frequency; F - Forehead tonic (DC) skin conductance level; G - Forehead phasic (AC) skin conductance spike amplitude RMS; H -Forehead phasic skin conductance spike frequency.

Table 2. Effects of ride time and day of experiment on heart rate, respiratory rate and finger and forehead skin conductance

	Before Ride (BR)	First minute of the ride	Last minute of the ride
Heart rate: ***(p=0.001 for time of ride factor, NS for the "day" factor***			
Day 1	79±3	88±3**	86±3**
Day 2	79±2	83±2	84±3
Day 3	79±2	83±2	84±4
Resp. rate ***p=0.037 for "time of ride" factor, NS for the "day" factor***			
Day 1	16±1	19±1*	18±2 ##
Day 2	16±1	18±1	16±1
Day 3	16±1	17±1	15±2
Finger tonic ***p<0.0001 for "time of ride" factor, NS for the "day" factor***			
Day1	7.6±1.4	16.2 ±2.1 **	19.7±2.0****
Day 2	8.8±2.0	14.3±1.9**	21.9±2.3 ****####
Day 3	5.4 ±1.3	9.8±1.8 *	17.7±2.0 ****####
Finger RMS: ***NS for "time of ride" factor, NS for the "day" factor***			
Day1	0.06±0.02	0.09±0.02	0.07±0.02
Day 2	0.01±0.005	0.04±0.01*	0.07±0.04
Day 3	0.07±0.02	0.04±0.01	0.10±0.04
Finger Frequency: ***NS for "time of ride" factor, NS for the "day" factor***			
Day 1	0.14±0.02	0.16±0.01	0.18±0.01
Day 2	0.14±0.02	0.16±0.01	0.11±0.01#
Day 3	0.09±0.02	0.13 ±0.03	0.17±0.02
Forehead tonic: ***NS for "time of ride" factor, NS for the "day" factor***			
Day 1	29.4±5.8	29.9±5.6	30.1±5.8
Day 2	21.9 ±3.7	23.1±3.7	28.9±3.5
Day 3	29.6±5.7	30.59±5.7	32.6±5.6
Forehead RMS: ***p=0.0001 for "time of ride" factor, NS for the "day" factor.***			
Day 1	0.006±0.002	0.015±0.005	0.061±0.020 **#
Day 2	0.004±0.001	0.010±0.004	0.024±0.008
Day 3	0.004±0.001	0.008±0.003	0.070±0.025***##
Forehead Frequency: ***p=0.0008 for the "time of ride" factor; NS for the "day" factor.***			
Day 1	0.08±0.02	0.08±0.02	0.12±0.02
Day 2	0.04±0.02	0.05±0.02	0.12±0.01**#
Day 3	0.05±0.01	0.08±0.02	0.11±0.02*#

*Data are presented as Mean ± S.E.M. Significance: *, ** and **** - p<0.05, p<0.01 and p<0.0001 compared to the time before ride; #, ## and #### - p<0.05, p<0.01 and p<0.0001 compared to the 1st min of the ride.*

2.3.5. Relations between nausea level and autonomic parameters

On the 1st day, there was a small but significant increase ($F(3, 56) = 2.808$, $p=0.048$, $\eta^2=0.30$) in HR during low-level nausea compared to "no nausea" condition; at higher levels of nausea the difference was not present (Fig. 6A). On the 2nd and 3rd days, there were no effects of nausea levels on HR. There was no effect of nausea rating on HR or respiratory rate for any of the three experimental days (Figs. 6B and Table 3).

On the 1st day, finger tonic SCL significantly and substantially ($F(3, 62) = 14.63$, $p<0.0001$, $\eta^2=0.41$) increased during nausea experience, and this increase correlated with nausea levels (Fig. 6C). This increase at all levels of nausea was preserved on the 2nd and the 3rd day (Table. 3). There was no systematic effect of nausea level on the finger RMS ($F(3, 62) = 0.5338$, $p=.6608$, $\eta^2=0.02$) or on the frequency ($F(3, 62) = 1.305$, $p=.28$, $\eta^2=0.05$) of finger SCL oscillations on any of experimental days (Table 3).

There was no dependence of forehead tonic SCL on nausea ratings on any of the three days ($F(3, 55) = 2.255$, $p=.0921$, $\eta^2=0.09$). Forehead RMS values were significantly ($F(3, 60)=2.626$, $p<0.05$, $\eta^2=0.11$) different for nausea levels >3 (Fig. 6G), and this difference persisted during 2nd but not the 3rd day. Finally, the greatest changes were observed in the frequency of the phasic forehead SCL events that increased substantially and significantly ($F(3, 62)=10.68$, $p<0.0001$, $\eta^2=0.34$) at all levels of nausea on all three days (Fig. 6H and Table 3).

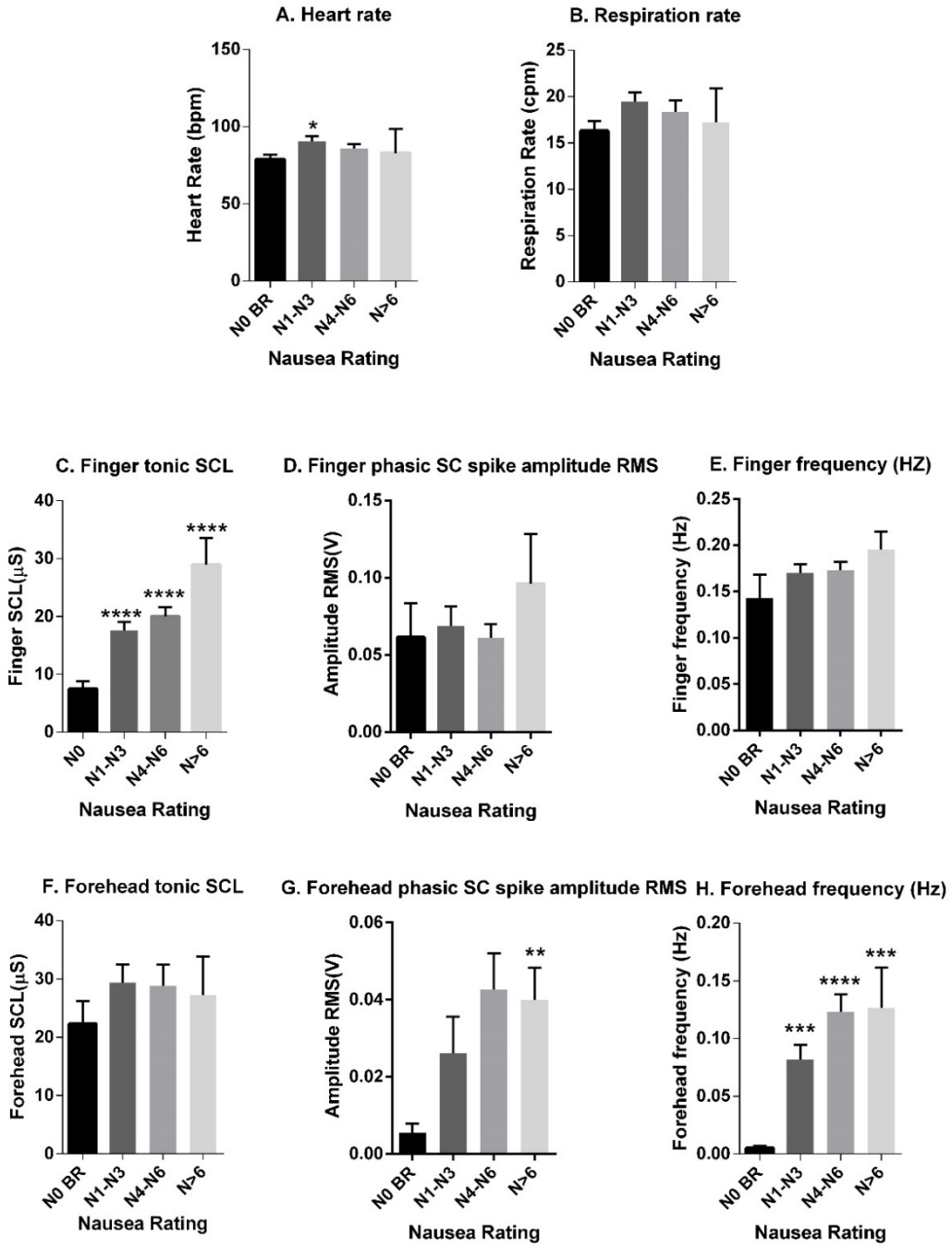

Fig. 6. Dependence between nausea ratings and physiological measures. A - Heart rate; B - Respiratory rate; C - Finger tonic (DC) skin conductance level; D - Finger phasic (AC) skin conductance spike amplitude RMS; E - Finger phasic skin conductance spike frequency; F - Forehead tonic (DC) skin conductance level; G -Forehead phasic (AC) skin conductance spike amplitude RMS; H -Forehead phasic skin conductance spike frequency.

Table 3. Effects of nausea levels on heart rate, respiratory rate and finger and forehead skin conductance.

	Before ride	N1- N3	N4-N6	N>6
HR: ***p=0.03 for "nausea" factor; NS for the "day" factor.***				
Day 1	78±2	90±3*	85±2	82±15
Day 2	79±2	82±1	81±2	79±3
Day 3	78±2	82±2	86±3	80±3
Respiratory Rate: ***NS for both factors***				
Day 1	16±1	19±1	18±1	17±3
Day 2	15±1	17±1	17±1	15±1
Day 3	16±1	15±1	14±1	16±1
Finger tonic: ***p<0.0001 for "nausea" factor, p=0.06 for the "day" factor***				
Day 1	7.5±1.3	17.6±1.4****	20.0±1.5****	28.9±4.5****
Day 2	13.9±0.8	16.1±1.3	19.8±1.2*	23.1±3.4**
Day 3	5.4±1.3	13.5±1.5**	15.2±2.0**	19.2±3.6****^{X}
Finger RMS: ***NS for "nausea" factor; p=0.0001 for the "day" factor.***				
Day 1	0.061±0.022	0.068±0.012	0.061±0.008	0.096±0.032
Day 2	0.014±0.005	0.027±0.004^{X}	0.027±0.004	0.039±0.014
Day 3	0.019±0.009	0.061±0.013	0.076±0.018^{Y}	0.040±0.012
Finger Frequency: ***NS for the "nausea" factor; p<0.0001 for the "day" factor.***				
Day 1	0.143±0.025	0.170±0.009	0.173±0.008	0.195±0.019
Day 2	0.143±0.025	0.118±0.008^{X}	0.097±0.009^{XXX}	0.086±0.021^{XX}
Day 3	0.096±0.020	0.109±0.010^{XX}	0.140±0.017	0.155±0.033
Forehead tonic: ***NS for both factors***				
Day 1	22.2±3.9	29.3±3.1	28.8±3.5	27.2±6.6
Day 2	21.6±3.4	23.8±2.3	20.8±2.6	23.1±2.2
Day 3	29.6±5.7	27.5±2.7	25.7±3.0	24.5±3.5
Forehead RMS: ***p=0.007 for "nausea" factor, p=0.01 for the "day' factor.***				
Day 1	0.005±0.002	0.026±0.009	0.043±0.009*	0.040±0.008**
Day 2	0.003±0.001	0.013±0.007	0.021±0.012*	0.020±0.006*
Day 3	0.004±0.001	0.004±0.001^{X}	0.009±0.004^{XX}	0.020±0.006
*Forehead Frequency****: p<0.0001 for "nausea" factor, NS for the "day" factor***				
Day 1	0.005±0.001	0.081±0.012***	0.12±0.015****	0.126±0.035***
Day 2	0.034±0.015	0.051±0.013	0.10±0.011**#	0.123±0.007**##
Day 3	0.045±0.012	0.057±0.008	0.11±0.017*	0.121±0.029*

*Data are presented as Mean ± S.E.M. Significance: *, **, *** and **** - p<0.05, p<0.01, p<0.001 and p<0.0001 respectively compared to "Nausea before ride" with no nausea point; # and ## - p<0.05 and p<0.01, respectively, compared to the "N1-N3" point; X , XX and XXX – p<0.05, p<0.01 and p<0.001, respectively, compared to Day1; Y – p<0.05 compared to Day 2.compared to Day 2.*

2.4. Discussion

Our study targeted autonomic changes and subjective symptoms that accompany cybersickness – a subtype of motion sickness elicited by immersion into virtual reality. There are numerous factors of VR technology that could be responsible for these alterations; generally they could be classified into two categories: hardware-dependent (a lag between head move and visual field move, monitor flicker, disaccord between vergence and accommodation) and content-dependent (6) In our case, the dominant contribution of the content (roller coaster ride) is evident from the fact that observing the static image during baseline period did not provoke any subjective discomfort. Motion sickness during the simulated ride likely occurred due to sensory visual-vestibular conflict: while rich imagery informed the brain about dramatic linear and angular accelerations, this information was not matched by afferent input from the vestibular and proprioceptive systems of the stationary subject.

Our major findings are that: i) cybersickness was associated with minor, if any, influences on HR and respiration but caused significant sudomotor responses; ii) subjective symptoms of cybersickness are long-lasting (>3h); and iii) repetitive provocations lead to prolonged ride tolerance and to the reduction of post-ride subjective symptoms (desensitization). Our results confirm and expand previous studies where phasic SCL events on the forehead were found to be the best physiological correlate of nausea induced by vestibular stimulations (9, 13). The subsequent discussion is focused on subjective symptoms of cybersickness and their habituation and on the finger-forehead differences of sudomotor responses.

2.4.1. Symptoms profiling of cybersickness

As noted above, the principal sensory input responsible for provoking cybersickness is visual, and this places cybersickness close to simulator sickness that has been extensively studied (8, 14). While simulator sickness shares many common symptoms with “classic” motion sickness, some subtle differences have been reported between them. Using a database of ten Navy simulators, (8)) concluded that symptoms such as drowsiness, decreased salivation, depression, faintness, stomach awareness, decreased appetite, confusion and vomiting can be eliminated from simulator sickness list of symptoms due to their infrequent incidence. We used in our study the original version of the MSAQ, and our results demonstrate that similar to other types of motion sickness (8, 15, 16) cybersickness is a multidimensional syndrome. We found that during cybersickness, gastrointestinal symptoms dominate (representing 37% of the total

score), followed by sopite (24%), central (24%) and peripheral (21%) clusters (see Methods for definitions), thus placing cybersickness close to vestibular-induced motion sickness. To the best of our knowledge, this is the first detailed profiling of cybersickness symptomatology with a well-validated psychometric instrument, MSAQ (8).

There is very limited research on the aftereffects of VR exposure. Using posturography, (17)) reported that immersion in VR produced mild and short-lasting postural instability. Another study (18) described potential aftereffects on visually guided behaviour and proprioception 30 minutes after exposure to VR. To the best of our knowledge, there is no research that investigate post exposure symptom dynamics for extended periods after experiencing VR. We found that following the first visual provocation, the central and sopite-related symptoms persist for at least 3h, gastrointestinal – for 2 and peripheral – for 1 h. This shortest lifespan of peripheral symptoms (predominantly based of sweating-related sensations) could be explained by the fact that excessive sweating mainly occurs during the presence of the provocative stimulus and quickly dissipates upon its termination (Fig. 4). Neural mechanisms responsible for long-lasting symptoms from other clusters remain to be elucidated. Habituation of cybersickness symptoms is discussed in the last section.

It must be noted that we have deliberately selected a highly provocative VR scenario for our experiment, and it may be that less provocative VR content would result in somewhat different spectrum of symptoms that most likely would not last for as long as the symptoms found in our study. It is also noteworthy that susceptibility to cybersickness varied greatly between subjects as determined both by subjective and objective measures. As none of our participants had any previous experience with VR, these differences were clearly unrelated to previous exposures. It is not excluded that differences in symptoms were in part due to potential differences in head movements during the ride. Lack of assessing this parameter is a study limitation; it is however unlikely that the amount of head movements contributed to sensory conflict, due to the very nature of the VR hardware that matched shifts in the visual field to head rotations preventing vestibulo-visual sensory mismatch.

2.4.2. Which autonomic changes accompany cybersickness, and why?

We observed a complex pattern of VR-induced autonomic effects: some responses (HR, respiratory rate and rise in finger SCL) occurred shortly after the onset of virtual ride when

nausea was not present. In contrast, forehead SCL responses occurred with some delay that was different between individuals but associated with development of nausea in most subjects. We interpret these findings as the evidence that VR simulation caused two separate effects with different time course, such that initial tachycardia, tachypnoea and finger sweating were the consequence of stress/hyperarousal provoked by the emotional exhilaration caused by the novel visual experience whereas delayed forehead sweating was related to gradually developing nausea. Indeed, finger SCL has been extensively studied by psychophysiologists, and it is well established and accepted that a rise in finger SCL reflects increased arousal (19, 20). Likewise, tachycardia and tachypnoea are common manifestations of stress/arousal (21-24). That rapid cardiac and respiratory responses were associated with novelty is also confirmed by the fact that they habituated and became non-significant on the 3rd day of the experiment. Finger SCL responses were more resistant and did not habituate reflecting higher sensitivity of this variable to visual provocation.

Differences reported here in the time course between forehead and finger sudomotor responses are reminiscent of the earlier work by McClure et al. (25) who simultaneously recorded SCL on the palmar and the dorsal regions of the hand during vestibular stimulation (Coriolis cross-coupling). This study reported that palmar sweating started within seconds after the onset of the provocative stimulation whereas sweating on the dorsal sweating developed with a delay and was associated with nausea. They interpreted these differences as “stress” (palmar) sweating being a response to novelty and as “thermal” (dorsal) sweating as a thermoregulatory disturbance associated with motion sickness (25). It is quite likely that these responses on the dorsum of the hand are homologous to the forehead sudomotor responses that we found in the current study. Overall, our results are in a good accord with the previous studies of MS evoked by different provocations, where sweating responses were prominent (9, 10) whereas cardiac, respiratory or pressor changes were either minor or absent (see (26) for review). The fact that small tachycardia found in our correlational analysis during low but not moderate and high levels of nausea (Fig. 6A) was likely caused by arousal, not nausea (see above). Furthermore, our results confirm previous findings by Golding (9, 10) who reported that during vestibular provocations, phasic sweating responses on the forehead were the closest correlate of nausea out of four combinations (finger vs. forehead and tonic vs. phasic SCL).

In all participants, we did not observe phasic SCL on the forehead during baseline; in contrast, in most subjects baseline finger phasic activity was present. Thus, responses on the forehead

appeared to be a consequence of predominantly *nausea-related* sudomotor sympathetic outflow whereas finger SCL changes seem to consist of three components: one related to baseline cognitive activity and/or oscillations in arousal levels, one due to stress/arousal induced by virtual ride, and one related to nausea. Because of this "contaminated" nature of the finger signal, the forehead should be considered as a preferred location for the studies that require objective quantification of nausea. This recommendation seems however to be not universal as several recent studies did report correlation between finger SCL and nausea levels (27, 28); the most likely explanation of this apparent discrepancy is that in the cited works nausea was elicited by means of optokinetic stimulation (slowly moving black/white stripes in the visual field) – a stimulus with (presumably) low arousing potential as evidenced by lack of finger SCL changes in a proximity of the stimulus onset (28).

Supporting other studies of cybersickness (29), another conclusion from our findings is that the pattern of autonomic changes that accompany cybersickness is similar to that reported during motion-induced MS. As already noted, previous studies reported that MS causes either minor or no changes in HR and respiratory rate but prominent rises in the SCL (9, 10, 27, 28), and one intriguing question is why such dramatic differences exist between perturbation of cardiovascular and respiratory systems on one hand and thermoregulatory system on the other? We attempted to answer this question in our recent review on association between motion sickness and thermoregulation (30). In brief, we expanded Treisman's idea of the "toxic" origin of nausea during MS (31); he suggested that the brain erroneously interprets a visual-vestibular mismatch as a sign of intoxication, and nausea provides a mechanism of aversive conditioning to prevent future intoxications. This "toxic" hypothesis perfectly explains thermoregulatory effects of MS as reducing body temperature during intoxication is an adaptive survival strategy as documented in a previous animal study (32). Looking at MS from this perspective, it becomes apparent that it is in fact associated with a complex integrative response including physiological (sweating, cutaneous vasodilation; see (30) for review), behavioural (cold-seeking (33)) and cognitive (altered perception of ambient temperature (33)) components that eventually leads to fall in body temperature (34). Confirming this hypothesis, we have recently discovered that provocative motion also elicits profound hypothermic responses in rats and musk shrews (35) and in mice (unpublished observation). In line with the above, changes in cardiac output or in minute ventilation do not present any evolutionary benefits during intoxication, and this potentially explains minor changes in HR and respiratory rate during MS.

2.4.3. Repetitive exposure to VR causes desensitization

Sensitivity to provocative motion could be reduced by repeated exposures to provocations with gradually increased intensity of stimulation. This approach is the basis of motion sickness desensitization programs used during pilot training (11, 12). Our study is the first to demonstrate that desensitization also occurs during virtual reality-induced motion sickness. Indeed, tolerated ride duration was substantially prolonged during the third session in our participants. While maximal nausea level was unchanged, the temporal course if its development was slowed down; this was paralleled by the gradual reduction of other symptoms as revealed by MSAQ scores. It must be noted that lack of between-days differences in our objective autonomic measures does not contradict the idea of desensitization as maximal nausea level did not change either. It is quite likely that a larger number of VR sessions would cause further desensitizing effects; the small number of sessions was the limitation of our study. It was caused by the lack of enthusiasm in our participants to repetitively experience the highly aversive sensation of nausea.

The fact that desensitization develops in response to both vestibular- and visually-induced provocations raises an intriguing question about the location of neural structures whose plasticity is responsible for the reduced sensitivity. There are at least two possibilities here: first, it may be that habituation occurs separately in afferent vestibular or visual pathways. An alternative explanation is that changes are in the central neural network responsible for the genesis of nausea; this network is currently actively studied (28, 36, 37). An indirect argument in favour of the latter suggestion is that sensitivity to motion predicts sensitivity to visual provocation (current study and (38)). Furthermore, there is a limited evidence of cross-desensitization, where repetitive sessions of optokinetic drum provocation resulted in prolonged reduction of susceptibility to seasickness (39).

2.4. Conclusions and perspectives

Supporting previous findings with different provocative stimuli, our work clearly demonstrates that assessing phasic SCL changes on the forehead is a reliable way to objectively quantify nausea levels. Further, we determined that repetitive exposure to provocative virtual reality content results in slowing down the speed of nausea development and in reducing other symptoms of cybersickness. While existence of cross-desensitization requires vigorous testing, it may be that virtual reality-based technology might represent a simple and cost-effective way

to reduce sensitivity to other types of nausea provocations. Lastly, while we deliberately selected for our study highly provocative VR content, our results indicate that modern VR technology is capable to inducing quite dramatic health problems.

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Chapter 3: Effects of visual flow direction on signs and symptoms of cybersickness

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By signing below, I confirm that Alireza Mazloumi Gavgani contributed to methodology and study design, recruiting, investigation, results analysis, visualization, writing the manuscript and corresponding to reviewers to the publication entitled Effects of visual flow direction on signs and symptoms of cybersickness.

A/Prof Eugene Nalivaiko

Abstract

Our objective was to assess the influence of visual flow direction on physiological changes and symptoms elicited by cybersickness. Twelve healthy subjects (6 male and 6 female) were exposed to a 15-min virtual ride on a rollercoaster on two different days in a counterbalanced manner, such half of participants were facing forward during the first ride while another half was facing backward. Forehead skin conductance, heart rate and HRV parameters (SDRR, RMSSD) were collected as objective measures; subjective symptoms were assessed with the Motion Sickness Assessment Questioner immediately after exposure. We found that while nausea ratings at which participants terminated the experiment did not differ between forward/backward rides, the mean ride tolerance time was significantly longer during reverse ride compared to forward ride (6.1±0.4 vs 5.0±0.5 min, respectively, $p = 0.01$, $\eta 2 = 0.45$). Analysis of HRV parameters revealed significant reduction in both RMSSD ($p = 0.02$, $t = 2.62$, $\eta 2 = 0.43$) and SDRR ($p = 0.01$, $t = 2.90$, $\eta 2 = 0.45$) in the forward ride; no such changes were found in the backward ride. We also found that amplitude of phasic changes in forehead skin conductance increased significantly in both ride directions. This increase however was significantly lower ($p<0.05$) in backward ride when compared to the forward ride. When assessed immediately post-ride, subjects reported significantly lower ($p = 0.04$) subjective symptom intensity after the reverse ride compared to the forward ride. We conclude that the direction of visual flow has a significant effect on the symptoms reported by the subjects and on the physiological changes during cybersickness.

Key words: virtual reality, nausea, cybersickness, skin conductance, sweating.

3.1. Introduction

Motion sickness (MS) develops when conflicting signals are received from the spatial orientation senses (1). This could either be visual/vestibular/proprioceptive conflict such as when on a boat in a rough sea or can be initiated within a single sensory system such as canal-otolith interaction during Coriolis cross-coupling (rotation around vertical axis with head tilts) (1), or by purely visual stimuli such as optokinetic drum (2). Apart from real motion, MS could be provoked by other means. Simulator sickness is frequently experienced by pilots who undergo simulator training (3, 4). Cybersickness is a form of MS which is provoked by exposure to virtual reality. The principal symptoms of MS are well known and include cold sweating, facial pallor and nausea with potential vomiting (5). Detailed previous studies however revealed that the list of MS symptoms is substantially longer. It is now accepted in

the field that MS is a multidimensional syndrome, and that all its symptoms could be split into four clusters: gastrointestinal (stomach awareness, nausea, vomiting); central (fainting, light headiness, disorientation, dizziness, sensation of spinning); peripheral (sweating, feeling hot) and sopite (annoyance, drowsiness, tiredness, uneasiness) (5). Individual's susceptibility to MS varies greatly and depends both on the scale of provocation and individual factors such as sex, age and ethnic background (6, 7). Additionally, there is now solid evidence suggesting that affective states such as anxiety may also contribute to MS susceptibility (8, 9).

Some studies have concluded that cybersickness induces more severe symptoms compared to simulator sickness (10). Cobb *et al.* (11) discovered that 80% of subjects experiencing virtual reality felt some level of nausea in the first 10 min of the exposure. There are various technical aspects of virtual reality that can contribute to the induction of cybersickness; they include field of view (12), exposure duration (13), mismatched motion (lag) between anticipated movement of visual field and the actual movement displayed in VR device (14). It appears however that the most critical factor contributing to the development of cybersickness is the content of virtual reality, in particular the amount of virtual motion. Not surprisingly, stationary visual scene was found to cause less symptoms compared to virtual oscillatory scene (15), and virtual double-axis rotation was more provocative compared to rotation around a single axis (16). Another aspect of visual content that deserves attention is the direction of virtual movement. Very little is known on this subject, and we were able to identify just one publication that addressed it (17). The authors presented to their subjects either expanding or contracting squares on a computer monitor, and found that expanding pattern (that elicited forward vection) caused more prominent MS and in larger number of subjects compared to contracting pattern (that elicited backward vection). Development of MS in this study cannot be explained in the framework of the classical "sensory conflict" theory as ideal constant linear motion would not elicit any sensations apart from visual, and thus there was no subject for a conflict. We thus aimed to test whether exposure to forward or backward virtual movement with multiple linear and angular accelerations, where vestibulo-visual conflict is apparent and inevitable, would have different effects. In our previous experiments we have established that out of several moving virtual environments, virtual ride on a rollercoaster is the most provocative one as only one of 14 volunteers managed to complete the ride while the rest terminated due to cybersickness (18).

Subjective rating of MS, like any psychometric score, lacks precision, and our secondary aim was to improve the accuracy of our study by adding objective physiological assessment. For this purpose, we monitored skin conductance level (SCL) – an index of sweating rate. In our previous experiments where we used identical provocation, we compared SCL changes recorded from finger and forehead, and found that finger location is not suitable for documenting nausea as responses in this area were initiated by highly-arousing onset of virtual ride, when nausea was still absent (18). In contrast, rise in SCL on the forehead did not occur until subjects reported mild/moderate nausea, similar to findings reported during vestibular provocations (19) . Furthermore, dramatic increase in nausea-related SCL phasic events on the forehead (>500% for the amplitude and >1000% for the frequency) was in sharp contrast with very moderate or no effect on heart rate or respiratory rate [18]. These finding indicate that forehead SCL is the most sensitive and relatively specific biomarker of nausea (providing potential effects of intense physical exercise or overheating are excluded). In conclusion, the aim of this study was to investigate the effect of direction of visual flow on the intensity signs and symptoms of cybersickness, with complementing nausea subjective score by quantification of forehead SCL.

3.2. Materials and methods

3.2.1. Participants and experimental design

The study was conducted in 12 healthy volunteers aged 27±6 y.o., 6 females and 6 males. The study protocol was approved by the Human Research Ethics Committee of the Newcastle University. The participants were randomly assigned to two groups (n=6 each); on two different days (at least one week apart) subjects experienced a virtual ride on a rollercoaster. The experiment was designed in a counterbalanced manner, so that participants from one group experiences forward ride on the first experimental day and backward ride on the second day, while the order was opposite in the second group.

On the day of arrival in the laboratory (air conditioned room kept at 21–22°C), after signing an informed consent, subjects completed the Motion Sickness Susceptibility Questionnaire, MSSQ (20). After fitting head-mounted virtual reality display (Oculus Rift DK1, Oculus VR, USA), a 5-min baseline recording of heart rate and forehead skin conductance was performed. During this period, a stereoscopic neutral image was displayed. Subsequently, the forward or reverse video rollercoaster ride (Helix, Archivision, NL) was active ted. The ride lasted for 15

min or until subjects felt too uncomfortable to continue, whichever came first. Subjects were asked to keep their heads as stable as possible during the ride. Subjects provided a verbal rating of nausea every minute, during the ride, on a scale from zero (no effect) to 10 (just about to vomit). After the ride, subjects completed the Motion Sickness Assessment Questionnaire, MSAQ (5).

3.2.2. Data acquisition and analysis

ECG was measured from the lead II of a 3-lead electrode configuration. Forehead skin conductance level (SCL) was measured using 8-mm silver/silver chloride gel-filled self-adhesive electrodes connected to the constant voltage Model 2701 BioDerm Skin Conductance Meter (UFI, Morro Bay, USA). The electrodes were placed on the right and left sides of the forehead 1 cm bellow the hairline, near the lateral corners of the eyes. All sensors were connected to a PowerLab 8 data acquisition system and a computer running Chart 8.0 (ADInstruments, Sydney, Australia). Sampling rate was 100 Hz for skin conductance signals and 1 kHz for ECG. Heart rate and two cardiac vagal indices (SDRR and RMSSD) were computed from the ECG trace for each minute of recordings using HRV module of the Chart 8.0 software. To compute the phasic component of the skin conductance, we applied a high pass-filter with a cut-off frequency of 0.05Hz (19). Chart software was also used to calculate the amplitude Root Mean Square (RMS) and frequency of the SCL phasic components.

Two types of analysis of physiological parameters were performed: i) dependence of measured variables on riding time; and ii) dependence of measured variables on nausea rating. As all participants terminated their ride at different times, we could not perform overall averaging of their data traces; instead, two points were selected for comparison: baseline (before the ride), and the last minute of the ride (i.e. when the nausea level was the highest). For the second type of analysis, data were split into “no nausea” (rating 0), “light nausea” (rating 1-3), “moderate nausea” (rating 4-6) and “strong nausea” (rating >6) bins.

Prism 7.1 (GraphPad, USA) was used for statistical analysis. Two-way ANOVA and T-tests for repeated measures were used to determine the effects of i) direction and time on physiological recordings and ii) nausea rating and direction on physiological recordings. T-tests for repeated measures were used to determine the effect of the ride direction on the slope of nausea rating vs. time relationship and effect of ride direction on ride duration period. The slope of nausea rise vs. time was determined by a linear fitting procedure according to the formula (Nausea rating = m x Time + c), where m is the slope; fitting procedure was performed

based on all available data points from each subject. Data are presented as means ± standard error of the mean (SEM). Statistical significance was set at $p<0.05$.

3.3. Results

3.3.1. Effects of virtual ride on nausea levels

Participants differed substantially in their MSSQ score; it ranged from 11 to 36 (mean = 19.7 ± 12.0). All participants reported vection and some level of nausea during the ride. None of the participants managed to complete the 15-min ride in either directions; however the mean ride tolerance time was significantly longer during reverse ride compared to forward ride (6.1±0.4 vs 5.0±0.5 min, respectively, $p = 0.01$, $\eta 2 = 0.45$, Fig. 1A). Average nausea rating was zero before the ride in both experimental days. In the backward ride only 33% of the participants reported high levels of nausea while in the forward ride this increased to 58% Fig. 1B. Although differences in average nausea ratings were not significant, there was a significantly lower maximal nausea rating when participants experienced reverse vs. forward ride (4.5± 0.6 and 5.5±0.5, respectively; $p = 0.014$, $t = 2.96$, $\eta 2 = 0.46$, Fig. 1C). There was also a significantly lower nausea rating vs. time slope during the reverse compared to forward ride (0.85±0.23 vs. 1.58±0.33 units/min, respectively, $p = 0.04$, $t = 2.23$, $\eta 2 = 0.33$; Fig. 1D).

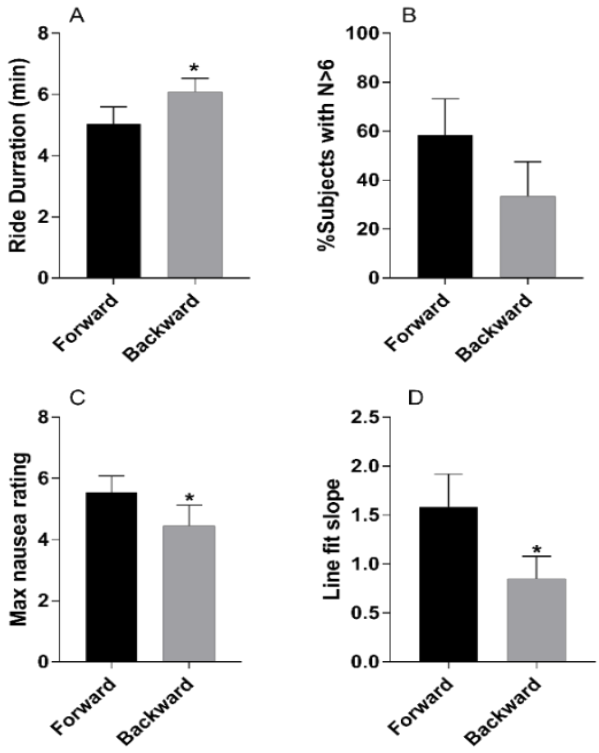

Fig. 1. Reverse direction prolongs ride tolerance time and reduces real-time nausea scores**.** A - Average ride duration in forward and backward rides. B - Number of subjects reporting high level of nausea. C - Maximum nausea reported during the ride. D – Average slope of linear regression for individual's nausea rating vs. time. * - *p<0.05*

3.3.2. Subjective symptoms induced by virtual ride

When assessed immediately post-ride, subjects reported significantly lower symptoms intensity after the reverse ride when compared to the forward ride (Table 1 and Fig. 2). Reverse ride direction was associated with significant reduction in total MSAQ score as well as with sub-scores in Gastrointestinal, Central and Peripheral symptom clusters. Sopite-like symptoms followed the same trend but the changes were not significant.

Table 1. Subjective symptoms of cybersickness depend on the direction of virtual ride.

	Forward (Mean±SEM)	**Reverse (Mean±SEM)**	**Significance**
Total MSAQ	0.47±0.05	0.32±0.05	p=0.04, t=2.75
Gastrointestinal	0.52±0.08	0.37±0.07	p=0.04, t=2.75
Central	0.56±0.07	0.36±0.05	p=0.002, t=3.7
Peripheral	0.47±0.06	0.30±0.07	p=0.009, t=3.2
Sopite	0.36±0.04	0.30±0.04	NS

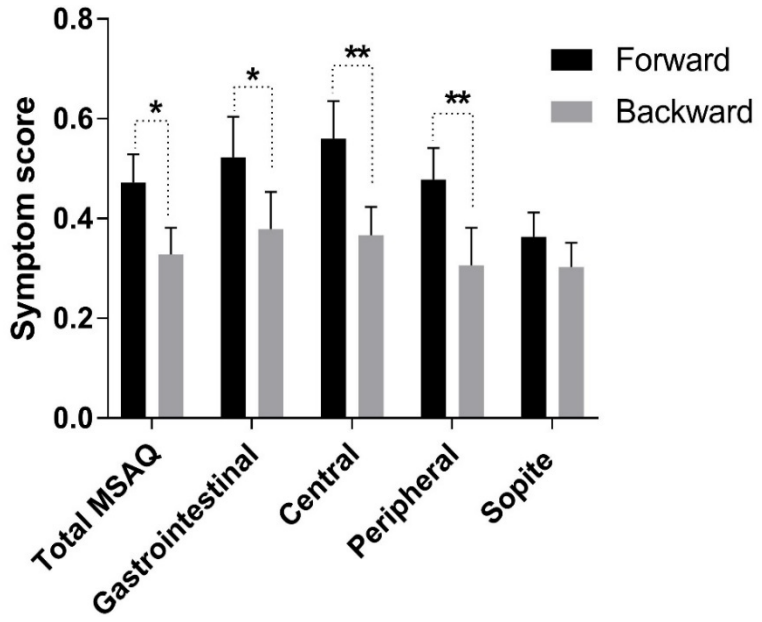

Fig. 2. Subjective symptoms of cybersickness depend on the direction of virtual ride**.** From left to right total: MSAQ score, gastrointestinal symptoms, central symptoms, peripheral symptoms and sopite symptoms. ** and ** - p<0.05 and p<0.01, respectively.*

3.3.3. Effects of virtual ride time on physiological parameters

In this analysis pre-ride physiological parameters were compared to the values obtained during the last minute of the ride, when participants reported their highest nausea scores. There was no difference in baseline heart rate values recorded during forward and backward ride, and no effect of the provocative VR exposure on heart rate (Fig. 3A). There were also no differences in baseline RMSSD and SDRR values in the two conditions. There was however a significant reduction in both RMSSD ($p = 0.02$, $t = 2.62$, $\eta 2 = 0.43$) and SDRR ($p = 0.01$, $t = 2.90$, $\eta 2 = 0.45$) in the last minute of the ride compared to baseline in the forward ride; no such reduction was found in the backward ride (Fig. 3B and 3C).

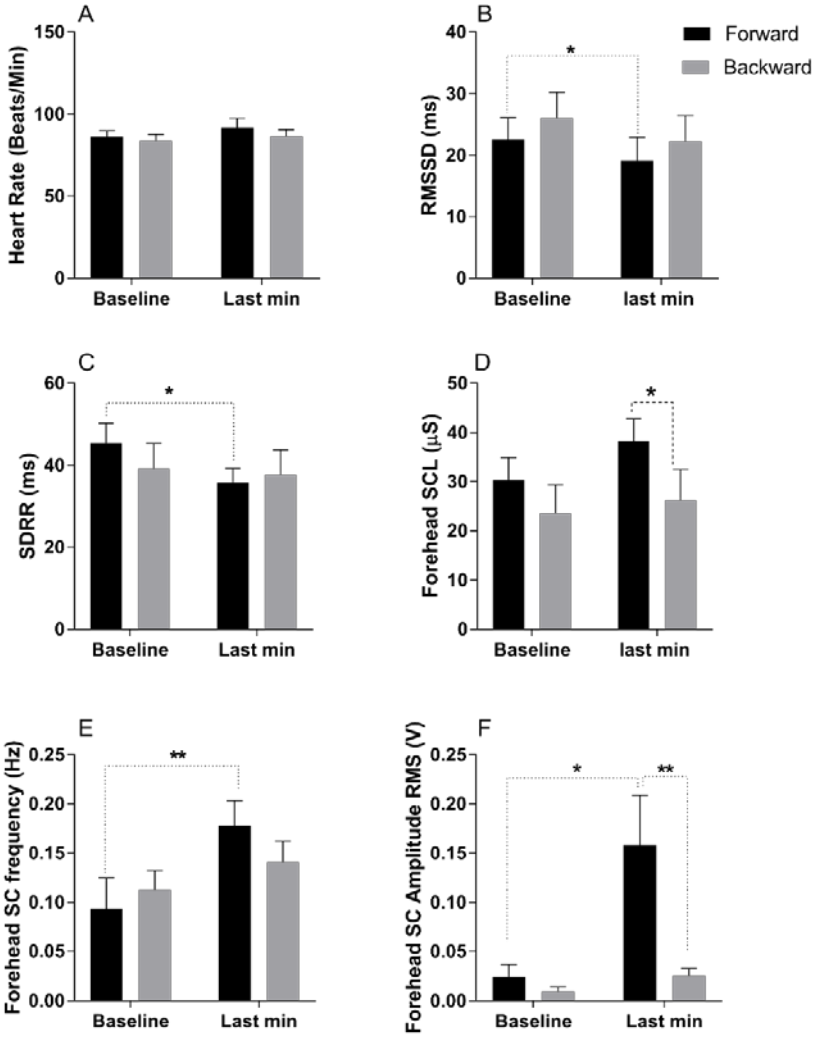

Fig. 3. Changes in physiological parameters during forward (black bars) and backward (grey bars) virtual rides. Each graph shows data values for the last minute of baseline period and for the last minute of simulated ride**.** A - Heart rate; B - Root Mean Square of the Successive Differences in R-R intervals (RMSSD); C - Standard Deviation of RR interval (SDRR); D - Forehead tonic (DC) skin conductance; E - Forehead phasic skin conductance spike frequency; F - Forehead phasic (AC) skin conductance spike amplitude RMS. * *and* ** - $p<0.05$ *and* $p<0.01$, *respectively.*

An example of the forehead SCL recordings obtained in one subject during a simulated ride is shown in Fig. 4. There was no, or minimal (<1 event/min), skin conductance activity during baseline on either of the days. Forehead skin conductance phasic events gradually appeared during simulated ride; this occurred at different times, and their appearance was clearly associated with nausea development as illustrated in Fig. 4. Frequency of spikes increased significantly ($p = 0.01$, $t = 3.13$, $\eta 2 = 0.49$) only in the forward ride while this increase was not significant in the reverse direction (Fig. 3E). Spike amplitude RMS value showed significant

increase in the last minute of the ride when compared to the baseline in the forward ($p = 0.03$, $t = 2.49$, $\eta 2 = 0.38$) and reverse ($p = 0.02$, $t = 2.68$, $\eta 2 = 0.39$) directions, however, in the reverse ride spike amplitude RMS value was significantly ($p = 0.01$) less when compared to the forward ride.

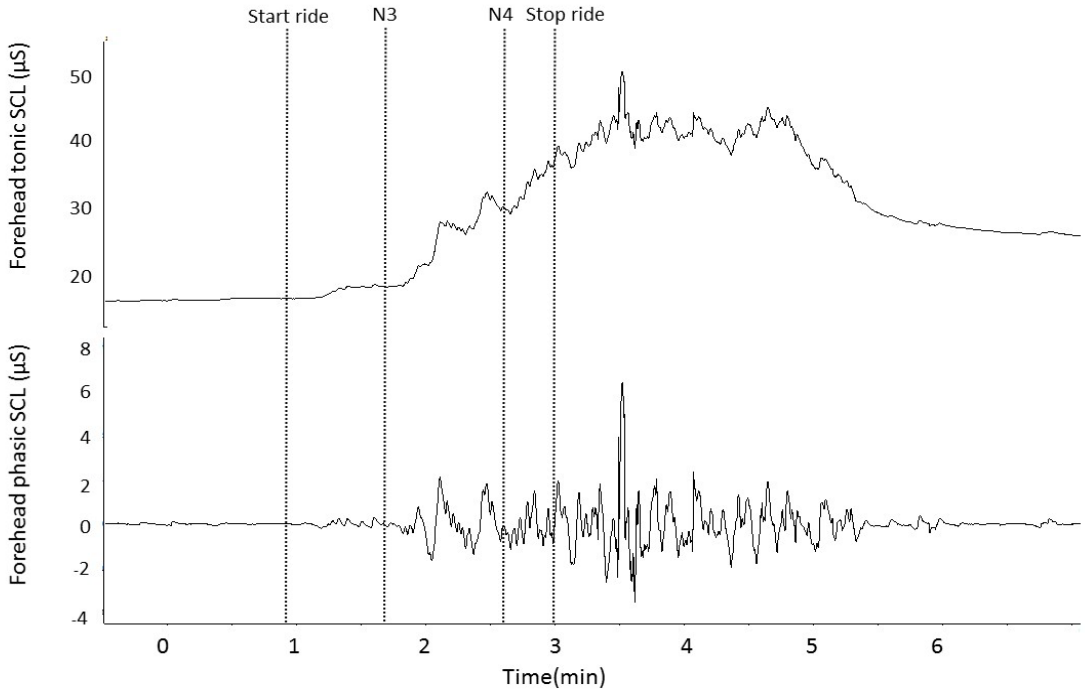

Fig. 4. Forehead skin conductance recordings obtained in one subject during simulated ride. Top trace – tonic SCL; bottom trace - phasic SCL. Vertical lines depict start/stop of the virtual ride and nausea ratings; prior to the ride onset nausea rating was zero.

3.3.4. Effects of nausea level on physiological parameters

RMSSD measure in the forward ride was inversely correlated with increasing nausea and reduced significantly ($p=0.001$, $F (3, 39) = 6.578$) in high nausea ($N>6$) ratings, Fig. 5A. There was no change in RMSSD measure in the reverse ride. SDRR changes did not show any correlation with nausea ratings in either of the ride directions, Fig. 5B.

Forehead skin conductance spike amplitude RMS increased significantly ($p=0.001$, $F (3, 34) = 6.428$) during nausea experience in the forward ride. This increase correlated with increasing nausea. The increase in spike amplitude was not significant in the reverse ride. The RMS spike amplitude decreased significantly ($p< 0.001$) in high nausea level ($n>6$) in the reverse ride compared to forward ride, Fig. 5C.

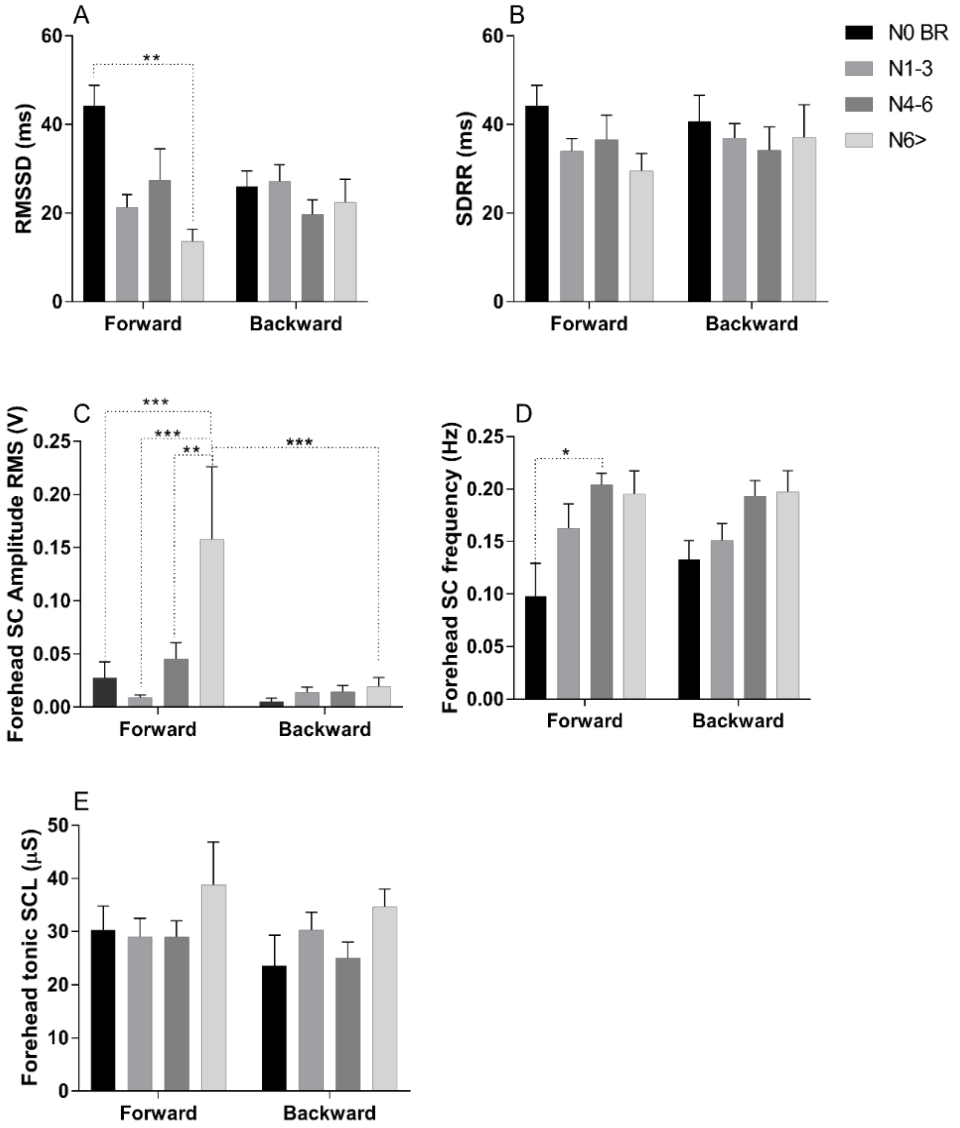

Fig. 5. Dependence between nausea ratings and physiological measures**.** A - Root Mean Square of the Successive Differences (RMSSD) B - Standard Deviation of RR interval (SDRR) C-Forehead phasic (AC) skin conductance spike amplitude RMS, D -Forehead phasic skin conductance spike frequency. E- Forehead skin conductance tonic values. *, **, ***- $p<0.05$, $p<0.01$ and $p<0.001$ respectively.

The frequency of forehead skin conductance events increased significantly ($p=0.015$, $F(3, 37) = 3.918$) during nausea experience in the forward ride. This increase correlated with increasing nausea. This increase in spike frequency was not significant in the reverse ride, Fig. 5D. Forehead tonic skin conductance events did not change in any of the ride directions, Fig. 5E.

3.4. Discussion

3.4.1. Effects of visual flow on subjective symptoms

The aim of the current study was to determine the effect of direction of visual flow on autonomic changes and subjective symptoms during exposure to provocative virtual motion. Our measures included both subjective rating and objective biomarker of nausea – forehead skin conductance that closely correlates with nausea levels during both real motion-induced and VR-induced motion sickness (18, 19). For assessing subjective symptoms, we utilized the well-established psychometric tool, MSAQ, that allows symptom classification in four different clusters (3, 21, 22). In line with our previous work, where we used just a forward virtual ride as a provocative stimulus (18), we found that the predominant MS symptoms were the gastrointestinal ones, followed by the sopite, the central and the peripheral symptoms (see Methods for definitions). In our current study we employed the same MSAQ immediately after exposure to the roller coaster ride in both forward and reverse directions. We found that there was a significant increase in all clusters of symptoms and in the total MSAQ score in both directions when compared to baseline. These finding are in accordance with previous observations (3, 18, 21) that cybersickness can result in a multidimensional spectrum of symptoms. We also found that motion sickness severity was less after backward compared to forward virtual motion exposure. Total MSAQ score and all but one of the symptom clusters scores showed a significant reduction after the backward ride when compared to the forward ride. Tolerated ride duration was substantially prolonged during the reverse sessions, with reflecting slower time course of nausea development; this was paralleled by the gradual reduction of other symptoms as revealed by MSAQ scores.

3.4.2. Effects of visual flow on autonomic parameters

We found that heart rate did not change with increasing nausea; this finding is in line with most previous studies (18, 19, 23) that reported minimum or no changes. We also assessed two HRV parameters, RMSSD and SDRR; both reflect vagally-mediated components of HRV and are associated with short-term changes in heart rate. Time-domain HRV parameters are generally calculated for a minimum of 5-min interval (24) however there are many studies confirming that values obtained from a shorter (1-min) intervals correlate well with the results calculated from a standard 5-min recording (25-28). Since the ride time in our experiments was dependent on the subject and many of the volunteers tolerated only few minutes of the ride, and also since the symptoms progressed rapidly, a 5-min recording was not suitable for this study, and we

used a 1-min epochs for computing HRV parameter. We found that RMSSD and SDRR decreased significantly during forward ride and remained unchanged during the reverse ride, suggesting that forward ride was associated with the suppression of cardiac vagal tone.
Previous studies, including our own, reported that phasic skin conductance activity in the forehead area is a reliable way of quantifying levels of nausea (18, 19). There was no or minimum phasic activity during baseline recording (at zero nausea ratings), and in majority of the subjects phasic activity started or augmented with increasing nausea. One of major findings in this study was that there was a significant increase in forehead spike amplitude and frequency in the last minute of the forward ride, when nausea ratings were maximal. Although average RMS signal increased in the reverse ride, this rise was not significant. Furthermore, changes in frequency of the phasic events were significantly higher in the forward direction of the ride when compared to the backward ride. These findings paralleled subjective ratings of nausea, which show higher nausea ratings in the last minute of the forward ride when compared to the reverse ride.

Our results thus represent the first report presenting evidence that moving forward in a motion-rich virtual context appears to be more provocative than moving backwards; this is reflected in both subjective and objective signs of cybersickness. In the following sections we present our view on the potential causes underlying this difference.

3.4.3. Ride direction as a provocative factor

Susceptibility to cybersickness varied substantially between our subjects as determined both by subjective and objective measures. As none of our participants had any previous experience with VR, these differences were clearly unrelated to previous exposures. It is not excluded that differences in symptoms were in part due to potential differences in head movements during the ride. Lack of assessing this parameter is a study limitation; it is however unlikely that the amount of head movements contributed to sensory conflict, due to the very nature of the VR hardware and software that matched voluntary induced shifts in the virtual visual field due to head rotations and tilts, thus preventing vestibulo-visual sensory mismatch. The true vestibulo-visual conflict was between virtual linear and angular accelerations and lack of corresponding sensations from the vestibular receptors.

There are various features of VR technology that could be responsible for inducing cybersickness; generally these factors can be classified into three classes: hardware-dependent (lack of head position tracking and visual field movement in XYZ planes, a lag between head move and visual field move, monitor flicker, disaccord between vergence and accommodation), content-dependent (29), and mismatch caused by subject movements. In our case, the dominant contribution of the content (roller coaster ride) is evident from the fact that observing the static image during baseline period did not provoke any discomfort. Throughout the experiment in forward and backward ride subjects were seated on a stationary office chair with limited movement capability, and thus their movement was limited to head movements or in some cases upper body movements. Since the main technical aspects (field of view, display resolution) of both forward and backward ride directions were identical, we conclude that the major factor responsible for differences in the "provocativeness" between the two conditions was the direction of visual flow.

3.4.4. Why forward ride is more provocative?

A possible explanation for the finding that forward virtual ride is more provocative than backward is that here there may be some parallels with the dependence of motion sickness on the ride direction in land vehicles in the real world. While we were not able to identify any research publication on this subject, it is common knowledge that sitting backward to the direction of travel often causes nausea; in fact it is not uncommon to find is social media (e.g. Trip Advisor) requests to advise how to book forward-oriented seats on trains. Whatever the mechanism of motion sickness in this latter case, it must be different from the one observed in the current study because sitting backwards in the virtual world appeared to be less, not more provocative.

It is quite probable that the core mechanism responsible for the phenomenon described in the current study may include some higher neural functions including complex cortical analysis of moving visual scene. Several previous studies explored effects of expanding and contracting geometric patterns that provoke sensations of forward and backward self-motion (vection), respectively. It appeared that the threshold for vection was lower for contracting patterns (17, 30), and providing vection is positively correlated to motion sickness (10), one would expect that a contracting pattern (simulating backward motion) would be more provocative. In contrast to this reasoning, but in accordance with our results, Bubka *et al.* (17) reported that an

expanding pattern was in fact more provocative. Precise neural mechanisms responsible for these differences are yet to be identified. Of note, results of described experiments do not fit into the framework of sensory conflict theory as linear motion at constant velocity does not elicit any vestibular activation and thus there is no condition for sensory mismatch.

An alternative explanation for the differences in the provocative effect of visual flow associated with its direction could be that during a forward-facing ride, anticipation of vigorous falls and turns that could be seen and anticipated in advance provoked hyperarousal locked with an anxiety- or fear-like state. The latter facilitated development of motion sickness induced by mismatch between intense visual flow and lack of vestibular sensations. Indeed, close association between anxiety and nausea is well documented: Tucker and Reinhardt (31) showed higher state anxiety in airsick students during flight training compared to non-airsick, and Collins and Lentz (32) reported a higher trait anxiety in motion sickness susceptible subjects. In a large community survey conducted by Haug *et al*. (33), among other risk factors, anxiety had the highest predictive power for nausea. This link between anxiety and nausea appears to be bidirectional as Eagger *et al*. found that patients with vestibular disease often report anxiety symptoms (34). In our previous study with identical virtual ride on a rollercoaster we found that ride onset was associated with moderate tachycardia and tachypnea reflecting arousal. Reduction of cardiac vagal HRV indices reported here during forward but not during backward ride supports the idea that the former condition was associate with anxiety state while the latter was not. There is rich literature linking reduced vagal tone to anxiety, and general consensus is that in subjects with affective disorders such as post-traumatic stress disorder, generalized anxiety and other anxiety disorders, time-domain vagal indices are reduced (35, 36). A meta-analysis on 36 relevant studies concluded that there is an overall reduction in HRV parameters in patients with various forms of anxiety disorders (37). It must be however acknowledged that cardiac vagal activity is also reduced by non-affective provocative visual stimuli (38).

3.5. Conclusions and perspectives

Our findings clearly demonstrate that the visual flow of the virtual stimulation has a significant effect on the symptoms reported by the subjects and the physiological changes during cybersickness. We propose the hypothesis that the underlying mechanism responsible for more provocative potential of the forward direction may involve anxiety-like state that potentiates

effects of sensory mismatch. It would be thus of major interest to test in future experiments whether there is an association between state anxiety and sensitivity to virtual motion.

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Chapter 4: Cybersickness-related changes in brain hemodynamics: A pilot study comparing transcranial Doppler and near-infrared spectroscopy assessments during a virtual ride on a roller coaster.

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Abstract

Our aim was to assess cerebral blood flow changes during cybersickness. Transcranial Doppler (TCD) ultrasound and near infrared spectroscopy (NIRS) were used separately in two independent experiments. In both studies, a 15-min virtual roller coaster ride was used as a provocative visual stimulus. Subjective nausea ratings were obtained at 1 min intervals. The TCD study was performed in 14 healthy subjects (8 males and 6 females); in this study we also measured heart rate and arterial pressure. In a separate study a 52-channel NIRS device (Hitachi ETG-4000) was used to monitor activated brain regions by measuring oxy-hemoglobin (HbO_2) concentration in 9 healthy subjects (4 male, 5 females). The TCD study results showed a significant increase in systolic (+3.8±1.8 mmHg) and diastolic (+6.7±1.3 mmHg) pressure at the end of the virtual ride (maximum nausea) compared to baseline (no nausea). We also found that middle cerebral artery (MCA) and posterior cerebral artery (PCA) systolic flow velocity decreased significantly at the end of the ride when compared to baseline values. Likewise, the relative systolic and diastolic conductance in the MCA decreased significantly (-0.03±0.02 cm x s^{-1} x $mmHg^{-1}$, t, p=0.0058 and -0.03±0.01 cm x s^{-1} x $mmHg^{-1}$, p=0.05, respectively) at maximum nausea when compared to no nausea. Additionally, there was a significant decrease (-0.02±0.01cm x s^{-1} x $mmHg^{-1}$, p=0.03) in the relative systolic conductance in the PCA at the end of the ride. Analysis of the NIRS results showed a significant increase in HbO_2 concentration in 15/52 channels in parieto-temporal regions of both hemispheres in participants who experienced motion sickness symptoms during the experiment. This increase in HbO_2 concentration correlated with increasing nausea and motion sickness symptoms. We conclude that cybersickness causes complex changes in cerebral blood flow, with an increase in perfusion in some cortical regions, but with a decrease of global cerebral perfusion.

Keywords: *motion sickness, nausea, virtual reality, cerebral blood flow.*

4.1. Introduction

Motion sickness (MS) is considered to be a general feeling of discomfort in ordinary routine life but also a major operational hazard for pilots and space agencies. It is currently well accepted that conflicting signals from the spatial orientation senses – visual, vestibular and proprioceptive leads to the development of motion sickness (1). This sensory conflict which was first described by Irwin (2) and later explained by James (3) in the early 19th century can be a result of single sensory system mismatch such as canal-otolith interaction during Coriolis cross-coupling, or between two or more sensory systems such as visual/vestibular/proprioceptive interference (4). These early findings suggest that the vestibular system plays a critical role in the pathogenesis of motion sickness (2). Other research has concluded that subjects with bilateral vestibular deficit are immune to motion sickness (3, 5); hence the vestibular system is indispensable in evolution of motion sickness. One potential cause of neuronal dysfunction responsible for motion sickness is alteration in regional cerebral blood supply; thus a close investigation of vestibular inputs in the regulation of cerebral blood flow is essential for better understanding the underlying mechanisms associated with motion sickness.

A recent study has found that people who suffer from motion sickness during parabolic flight are more likely to have orthostatic intolerance and increased cerebrovascular resistance after flight (6). Serrador et al reported an increase in cerebrovascular resistance and decreases in cerebral flow velocity minutes before any motion sickness symptom was experienced in an experiment where subjects were rotated in a human centrifuge (7). A study by Heckmann (8) found that caloric vestibular stimulation of the semicircular canals increases blood flow in the basilar artery. A similar study utilizing caloric stimulation reported an increase in the middle cerebral artery (MCA) blood flow while a significant decrease was seen in the flow in the posterior cerebral artery (PCA). These researches suggest that cerebral blood flow (CBF) changes with increasing nausea and motion sickness.

There are several methods to assess CBF; in recent studies a link between the neural metabolism and perfusion in the brain has been demonstrated using devices such as single photon emission computed tomography(9), positron emission tomography (10) and the xenon-133 inhalation technique (11). Transcranial Doppler (TCD) ultrasound is another device that has been widely used as a screening tool in monitoring perfusion in stroke (12-14), trauma (13), screening lesions (15, 16) and other studies concerning the hemodynamic changes in the brain

such as MCA blood flow during diverse stimulation maneuvers, viz. cycling, reading and writing (17), or flow alteration in Posterior Cerebral Artery (PCA) (18). Another technique which is extensively used in observing CBF is near infrared spectroscopy (NIRS). This device uses the basic concept of emission of near-infrared light (NIR) at the surface of the head and detection of reflected light at a distance of a several centimeters to determine hemoglobin concentration in the cerebral cortex. Due to the non-invasive nature and simple application of the NIRS device, this tool has been utilized in various aspects of brain imaging. Some studies have used this tool to monitor brain injury and ischemic regions in the brain looking at regional cerebral blood flow in brain-injured patients (19), others have employed this tool to screen brain activation regions while performing certain mental (20, 21) and physical (22, 23) tasks. NIRS has been used to closely monitor brain blood flow in other neurogenic diseases such as dementia, Alzheimer's (24), schizophrenia (25) and infant brain studies (26, 27). Several previous studies have shown close correspondence between fMRI and NIRS signals with significant spatial and temporal correlations (28) (29).

However, the inherent limitation of these screening methods when used in conjunction with physical motion sickness provocation – motion artifacts and other major technical restrictions- have constrained the application of these technologies in assessing CBF during motion sickness. To overcome this limitation, in this study we have adopted a standardized virtual reality (VR) provocation method to elicit motion sickness. Although motion sickness is characterized by a physical sensation of motion, exposure to VR provokes similar symptoms to motion sickness. This is caused by the feeling of movement in a virtual environment while being stationary. Cybersickness is relatively common, and most people feel some level of sickness during a provocative VR experience. A study on cybersickness symptoms discovered that 80% of subjects experienced symptoms of cybersickness in the first 10 minutes of their VR exposure (30). In our previous studies where we used a simulated ride in a rollercoaster, with vigorous linear and angular accelerations, we found that all participants developed some level of nausea and/or other motion sickness symptoms during this provocative exposure (31, 32). Some of the most common symptoms related to cybersickness were nausea, dizziness and disorientation that are similar to “classical” motion sickness symptoms.

The objective of this study was to examine temporal changes in cerebral blood flow in subjects who experience nausea during visually induced motion sickness. TCD and NIRS were used to study the changes in global and local CBF, respectively. To our knowledge these techniques

have not been used to investigate brain hemodynamics during cybersickness. We hypothesized that blood flow would decrease in subjects who experience cybersickness symptoms. We also expected to see an increase in Posterior Cerebral Artery (PCA) blood flow due to activation of the visual cortex in response to visual provocation. We also anticipated that NIRS results would be consistent with TCD data and will demonstrate a decrease in cortical blood flow in subjects who develop motion sickness.

4.2. Methods

4.2.1. Participants

This study was conducted in two groups of young healthy subject with the approval of the Newcastle University Humans Research Ethics Committee. The exclusion criteria were history of vertigo, vestibular dysfunction or neurological disorders as well as ortostatic intolerance. All subjects verbally confirmed that they are healthy and not using any medication. Cerebral blood flow velocity was measured by trans-cranial Doppler (TCD) ultrasound in 14 volunteers (8 males and 6 females, average age 28±7.0 y.o. range 19-48 y.o.). Cortical blood flow was measured by functional near-infrared spectroscopy (fNIRS) in another group of 9 volunteers (4 male, 5 female, average age 33.3±5.4 y.o., range 26-42 y.o.)). All participants were exposed to visual provocations leading to motion sickness (visually-induced motion sickness, VIMS). All participants gave informed written consent and completed a Motion Sickness Susceptibility Questionnaire (33) before the experiment started.

4.2.2. Cerebral blood flow recordings

In the TCD monitoring experiment, after fitting a head-mounted VR display (Oculus Rift DK2, Oculus VR, USA), the 2 MHz TCD probes were placed bilaterally on the head and adjusted to obtain optimal flow signals from the MCA on one side and from the PCA on another side. The probes were connected to the TCD ultrasound device (DWL, Germany) that has a 100 Hz sampling rate.

The other group of participants were fitted with a skullcap containing 52-channel fiber-optic probes. We used an optical topography system (ETG-4000, Hitachi Medical Corporation, Japan) for the NIRS measurements. Designed for comfort and flexibility, the skullcap holds the sensors and detectors in place and secures the probes in precise locations around the

subjects' head. The light source optical fiber tips are 'sprung', ensuring continual scalp contact for accurate readings. This device uses continuous laser diodes with two wavelengths, 695 and 830 nm, as light sources; the transmitted light signal is sampled every 100 ms.

4.2.3. Experimental setup, data collection and analysis

Before virtual ride commencement, a baseline 5-min recording was performed. During this period, a neutral static image was presented on the rift display. Subsequently, a simulated Helix rollercoaster ride (Helix, Archivision, Netherlands) was activated. The ride lasted for 15 min or until a subject decided to stop due to discomfort, whichever occurred first. During the experiment, subjective nausea ratings were assessed every minute using 10-point scale from zero (no nausea) to nine (just about to vomit). All recordings continued for 5 min after the ride termination. In the TCD study we also assessed heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure at the beginning and then every 2 minutes in the experiment using a cardiovascular profiling instrument PulseWave CR2000 (Hypertension Diagnosis, USA).

In the TCD experiment, systolic and diastolic TCD data were transferred into the Lab Chart 8.0 software (AD Instruments, Sydney, Australia) for analysis. As all participants terminated the ride at different times from the onset, overall averaging for their flow traces was not possible; thus, for comparison we selected two data points: "Baseline" (an average of the 2^{nd} and 4^{th} min of control period) and "End Ride" data from the last minute of the ride. Relative conductances of the MCA (C_{MCA}) and PCA (C_{PCA}) were computed according to the formula: $C_{MCA} = V_{MCA}/AP$ and $C_{PCA} = V_{PCA}/AP$, where V represents blood flow velocity in cm/s. Flow data values for these calculations were taken from 30 sec before to 30 sec after each AP and HR measurement. Statistical analyses were performed using Prism 7.0 (GraphPad, USA). Correlations between the subjective nausea ratings, ride duration and MSSQ score were assessed using Spearman's correlation. Paired t-tests were performed to determine the effect of cybersickness on HR, AP and MCA and PCA conductance. Two-way ANOVAs were performed to assess differences between time points and sex effects. Sex differences in ride duration, MSSQ and maximum nausea ratings were assessed using unpaired t-tests.

In the NIRS setting, digital data containing oxygenated haemoglobin (HbO_2), deoxygenated hemoglobin (deoxy-Hb) and total Hb values were transferred into Excel where initial analysis was performed. Our primary measure was oxy-Hb levels reflecting regional brain activity.

Thirty seconds (300 samples) immediately prior to each subjective nausea rating were extracted and averaged for every channel. All 52 channels were analyzed individually for every subject. For the analysis of relationships between NIRS changes and nausea, data were grouped into "no nausea/baseline" (rating 0), "light nausea" (rating 1-3), "moderate nausea-strong" (rating 4-7) bins. Statistical analysis was performed using Prism 7 (GraphPad, USA). Sidak's multiple comparison one-way ANOVAs were performed to determine the effects of nausea on HbO_2 concentration. Correlations between the subjective nausea ratings, ride duration and MSSQ score were performed as described above. Data is presented as means ± standard error of the mean (S.E.M.). Differences between males and females were assessed by means of unpaired Student's t-test. Statistical significance was set at $p<0.05$.

4.3. Results

4.3.1. TCD study

The participants had a substantially varying MSSQ score ranging from zero to 29 (mean 13.7±3.7). No nausea was reported by any subject during the baseline recording. During the ride, all participants reported some level of nausea that gradually increased with time. Eleven out of 14 participants terminated early (<15 min) due to discomfort. The average nausea rating in the last minute of the ride was 3.5±0.7; mean ride duration was 10±1.7 min.

There was a significant correlation ($r^2= 0.38$, $p=0.01$) between the subjective maximum nausea rating and MSSQ (Fig. 1A), also a significant negative correlation was stablished ($r^2=0.30$, $p=0.04$) between the tolerated ride duration and MSSQ score (Fig. 1B).

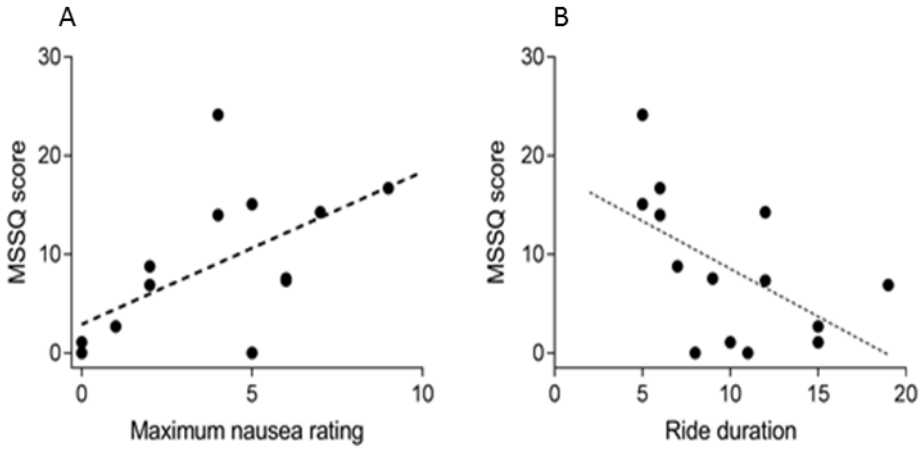

Fig. 1. Relationship between MSSQ score and maximum nausea rating (A) correlation of tolerated ride time and MSSQ score (B). Dashed line shows result of linear regression.

There was a significant increase in heart rate (+5.8±2.4 bpm, t (13)=2.4, p=0.01) at the end of the ride compared to the baseline (77± 2.9 bpm, Fig. 2A). SAP and DAP also significantly increased (+3.8±1.8 mmHg, *t*(13)=2.10, p= 0.02 and +6.7±1.3 mmHg , *t* (13)=4.95, p<0.001, respectively; Fig. 2B and C) at the end of the ride when compared to baseline values (118.9±3.7 and 67±2.9 mmHg, respectively).

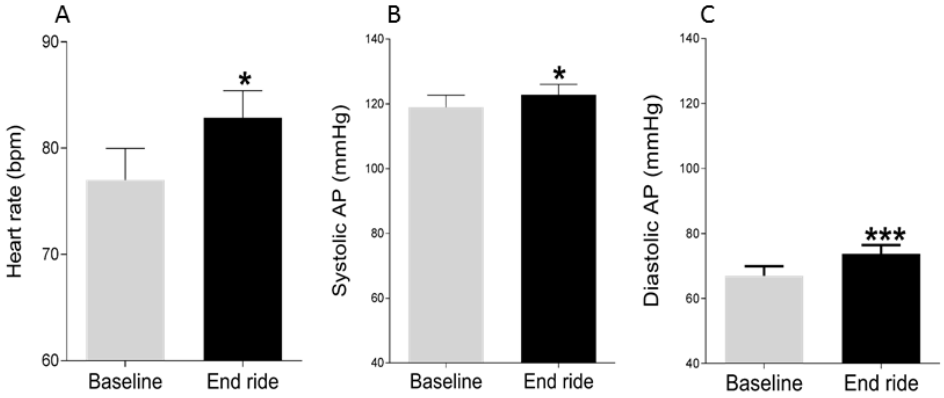

Fig. 2. Differences in HR (A), systolic arterial pressure (B) diastolic arterial pressure (C) between baseline and the last minute of the ride when nausea was maximal. * - *p<0.05 compared to baseline; *** - 0.001 compared to baseline*

The PCA systolic flow velocity and conductance decreased significantly (- 5.15±2.42 cm/s, p=0.05 and-0.02±0.01cm x s^{-1} x $mmHg^{-1}$ p=0.03) at the end of the ride with maximum nausea when compared to baseline (Fig. 3A &B). PCA diastolic velocity and conductance did not show any significant change to baseline values at the end of the ride (Fig. 3 C&D).

There was a significant decrease in MCA systolic velocity and conductance (- 5.15±2.42 cm/s, p=0.05 and -0.02±0.01cm x s^{-1} x $mmHg^{-1}$ p= 0.005, respectively) at the end of the ride when compared to the baseline, Fig. 3E&F. The diastolic MCA velocity remained unchanged (Fig. 3G). The diastolic MCA conductance decreased significantly (-0.03±0.01 cm x s^{-1} x $mmHg^{-1}$, p=0.05) in the end of the ride (Fig. 3H).

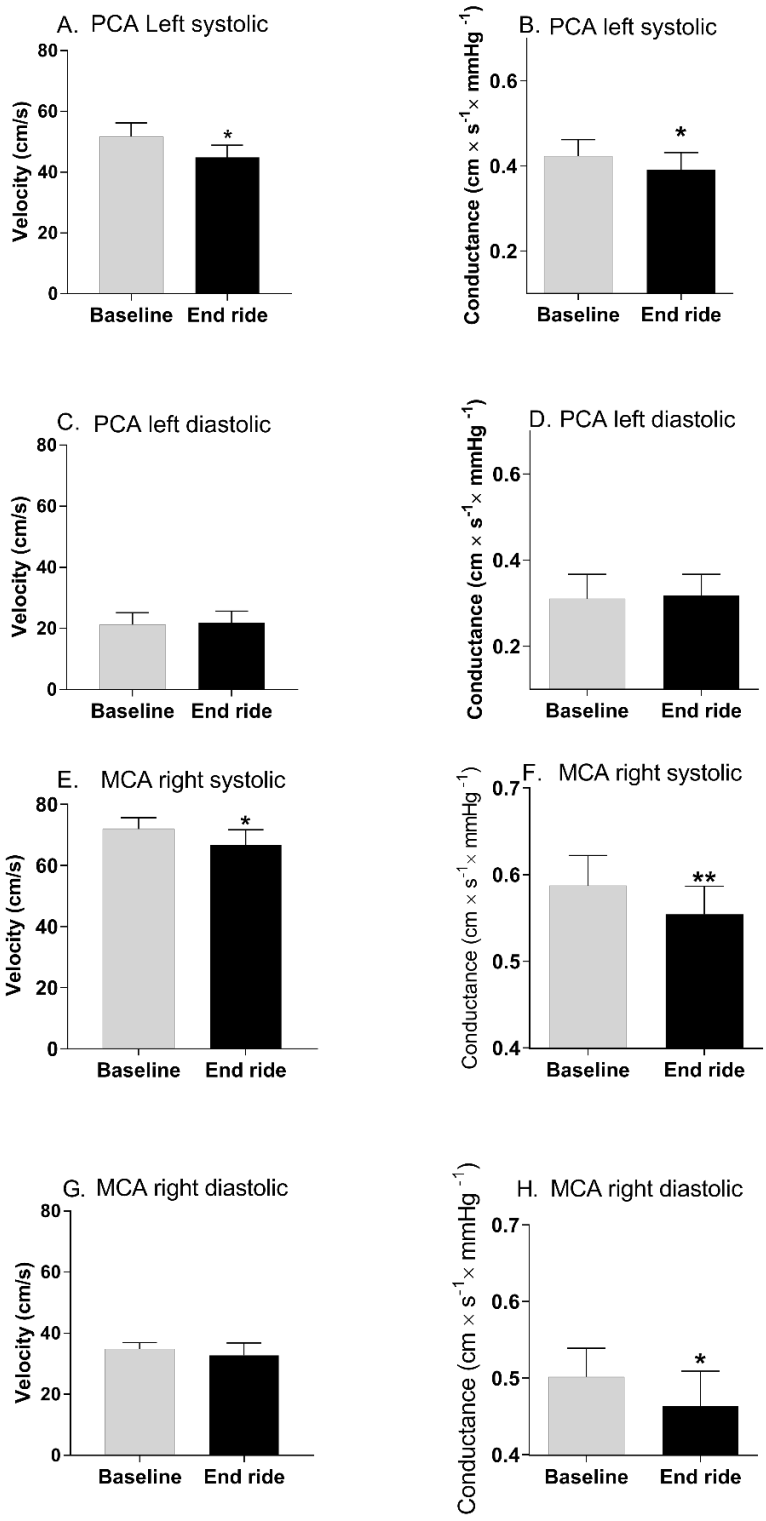

Fig. 3. Changes in velocity and conductance at baseline and the last minute of the ride (when nausea was maximal). A - PCA systolic velocity B - PCA systolic conductance, C- PCA diastolic velocity, D- PCA diastolic conductance, E- MCA systolic velocity, F- MCA systolic conductance, G- MCA diastolic velocity, H- MCA diastolic conductance. PCA velocity and conductance are measured from left side, MCA velocity and conductance are measured from the right side * - *$p<0.05$*, ** - *$p < 0.01$ compared to baseline.*

The increase in heart rate showed a significant positive correlation (r^2 = 0.51, p=0.005) with the reported nausea ratings (Fig. 4A). SAP level followed the same trend and a significant positive correlation (r^2 =0.43, p= 0.01) was stablished with subjective nausea ratings reported by the participants during the ride (Fig. 4B). Systolic MCA velocity showed a significant negative correlation (r= -0.36, p= 0.05) with nausea ratings (Fig. 4C).

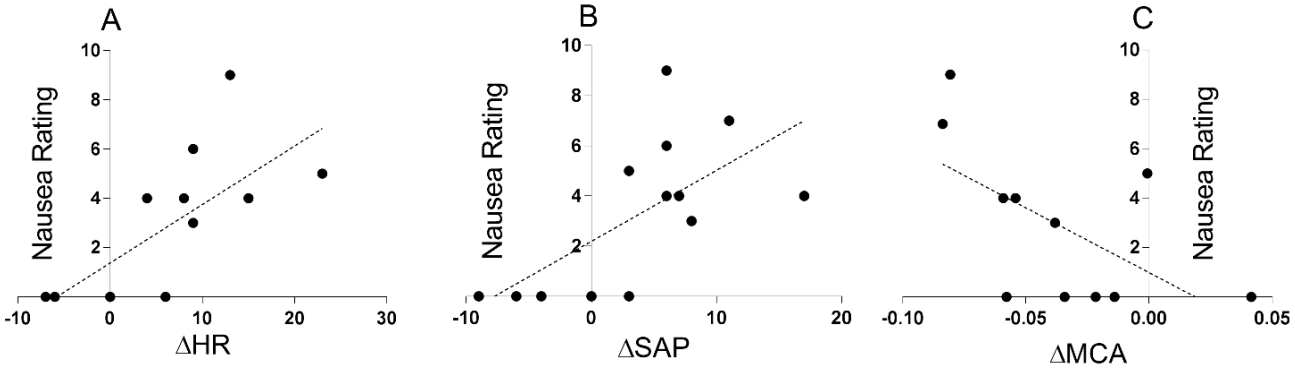

Fig. 4. Correlation between changes in Δ Heart-rate (A), ΔSAP (B), Δ MCA systolic velocity (C) and nausea ratings.

4.3.2. NIRS study

In the NIRS study, the MSSQ score varied significantly between subjects ranging from zero to 50 (mean 24.6±16.3). Nausea was not reported by any of the subjects during the baseline recordings. However, 8/9 subjects reported some level of nausea during the ride that gradually increased with time. Only one subject did not experience nausea or any form of motion sickness symptoms. This participant completed the 15-min ride designated for this experiment. The average nausea rating in the last minute of the ride was 4.8±2.2, and the mean ride duration was 7.5±1.7 min.

There was a significant positive correlation between the MSSQ score and maximal nausea level (r^2 = 0.58, p=0.01, Fig. 5A) and significant negative correlation between MSSQ score and ride duration (r^2 = 0.50, p = 0.03, Fig. 5B).

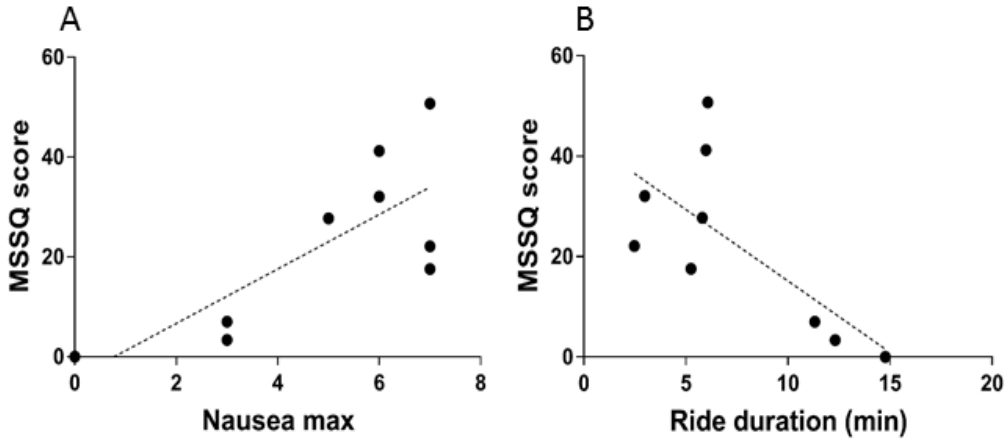

Fig. 5. Relationship between MSSQ score and maximum nausea rating (A), tolerated ride duration and MSSQ (B)

Analysis of NIRS results revealed significant increases in HbO_2 concentration in parieto-temporal regions of both hemispheres in participants who experienced motion sickness symptoms during the experiment. These regions corresponded to 15/52 channels (eleven channels on the left hemisphere, four channels on the right hemisphere) as illustrated in Fig. 6A). There was no significant change in cortical HbO_2 concentration in one volunteer who did not experience nausea or any form of motion sickness symptoms.

In subjects who were susceptible to motion sickness, average oxy-hemoglobin concentration increased significantly with increasing subjective nausea ratings ($p=0.01$, $F(3, 35) =3.79$). Group data for changes in HbO_2 for one of the "sensitive" channels (Ch. 40) are presented in Fig. 6B. Despite following the same trend, changes in HbO_2 concentration in 13/52 channels were not statistically significant (channels in orange color, Fig. 6A); most of these channels were adjacent to "hot" channels. Group data for changes in HbO_2 for one of such channel (Ch. 45) are shown in Fig. 6C. As also could be seen in Fig. 6A, the rest of the channels (24/52) did not show any correlation between the increasing nausea and perfusion in the cortex; they are shown in green; group data for changes in HbO_2 for one of such channel (Ch. 11) are presented in Fig. 6D.

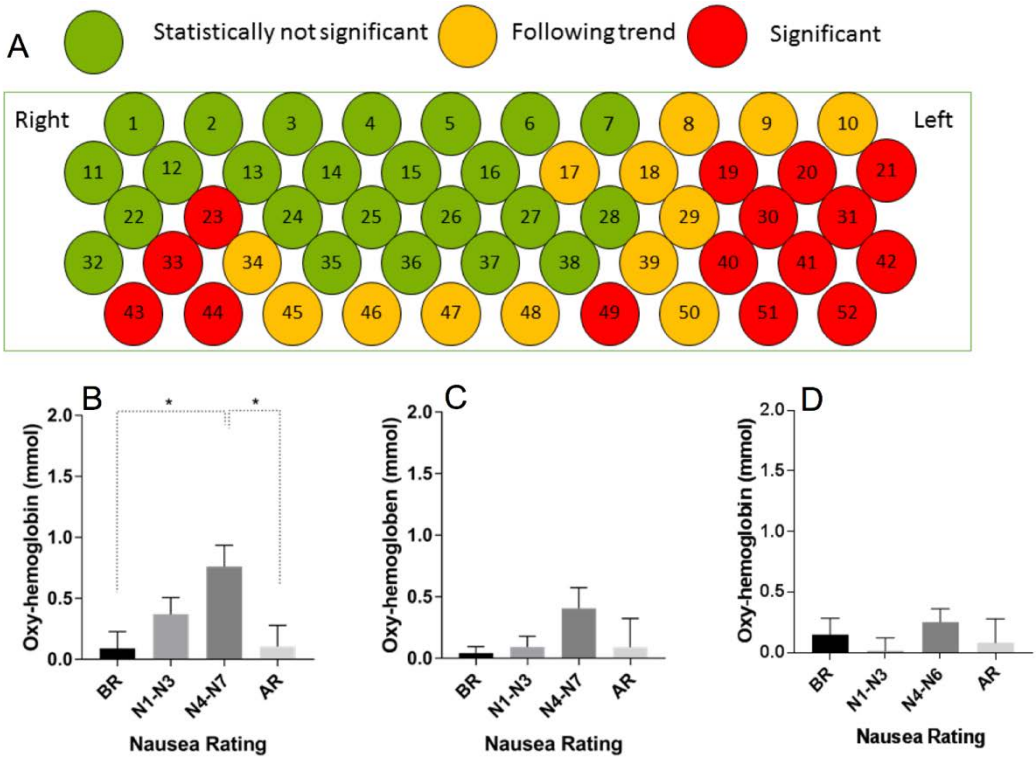

Fig. 6. Changes in cortical blood flow induced by VR provocation. A - NIRS channel scheme demonstrating channels with significant changes in hemoglobin concentration (red), channels following the trend but not significant (orange), and channels without changes (green), B - Oxy-Hb concentration in channel 40 plotted against subjective nausea ratings during the VR roller coaster ride. C- Channel 45, D- channel 11. In B-D, data values are pooled for four conditions: before ride (BR), mild nausea (N1-N3), moderate/strong nausea (N4-N7) and after ride (AR). * - $p<0.05$

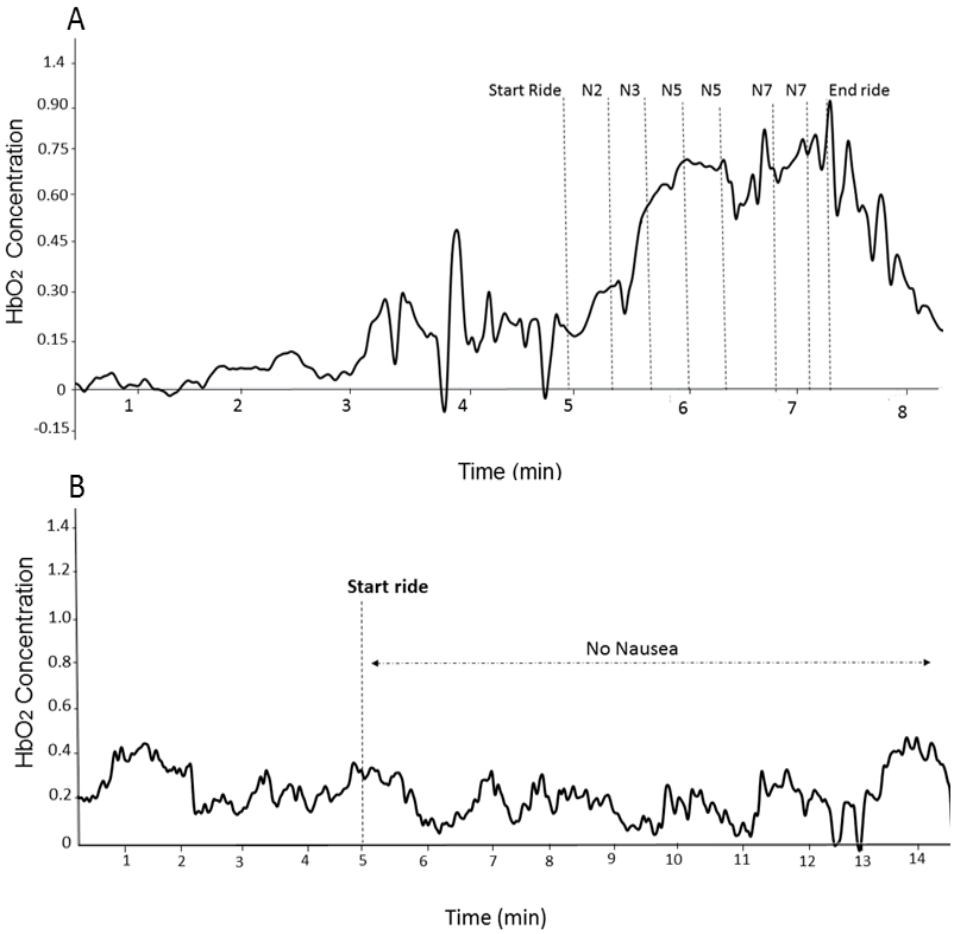

Fig.7. HbO_2 concentration from channel 40 during the VR provocation experiment in the subject with high level of nausea (panel A) and in the subject with no nausea (panel B). Note that in the susceptible subject, the HbO_2 value gradual increases with the onset of nausea, peaks at the time when nausea rating was maximal, and then gradually returns to the baseline. Vertical dashed lines depict ride onset/end and nausea (N) scores.

Two raw records of temporal changes in HbO_2 concentration are presented in Fig. 7. The record shown in Panel A was obtained from Ch. 40 in one of the susceptible individuals. It could be seen that HbO_2 gradually increased with the onset of nausea, and returned to the basal level within several minutes after ride termination. The record in Fig. 7B (also Ch. 40) is from the subject who did not experience any nausea; in this case there were no changes in HbO_2 levels.

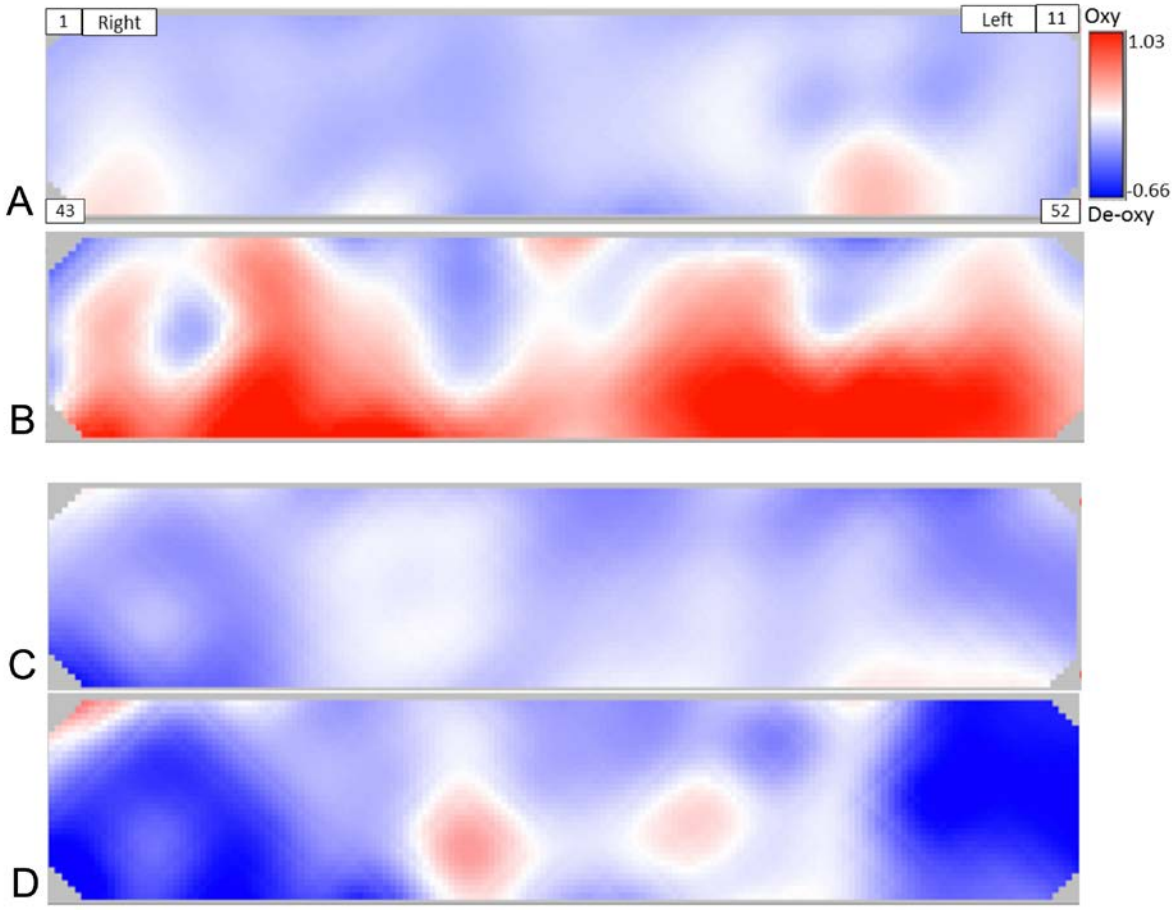

Fig. 8. Changes in HbO_2 concentration during VR provocation in a susceptible subject (A-B) and in a resistant subject (C-D). The panels show 2D topographic images of NIRS signal before the ride onset (A,C) and at the highest level of nausea (B) or before ride termination (D). Inset – pseudo-color scale of HbO_2 concentration.

Two-dimensional topographic images of all the NIRS channels recorded during the VR experiment are displayed in Fig. 8. The upper panels (A&B) illustrates dramatic changes in cortical blood flow in an individual who terminated his virtual ride at nausea level 7. The bottom panels (C&D) are from the subject who did not experience any nausea; his cerebral blood flow remained largely unchanged.

Table 1 presents spatial relationship between channels that were activated in our study and relevant cortical areas. The data are compiled based on the study Sato et al. (21) that employed identical channel setup. It could be seen that activated regions correspond mostly to the temporal, frontal and parietal lobes on the left side and to the temporal lobe on the right side.

Table 1. Estimated location of each NIRS channel and corresponding Brodmann area (BA) numbers are shown for each channel.

NIRS channel Left	# BA Area	Brodmann Area
		Left
19	44	Inferior frontal gyrus (Pars opercularis)
20	1, 43	Primary Somatosensory Cortex- 43 Primary gustatory cortex
21	40	Supramarginal gyrus
30	6	Premotor cortex and Supplementary Motor Corte
31	2,43	Primary Somatosensory Cortex, 43 Primary gustatory cortex
40	45	inferior frontal gyrus (Pars triangularis)
41	43	Primary gustatory cortex
42	22	Superior temporal gyrus Wernicke's area
49	10	Anterior prefrontal cortex
51	48, 38, 21	Retrosubicular area, Temporopolar area, Middle temporal gyrus
52	21	Middle temporal gyrus
		Right
23	6	Premotor cortex and Supplementary Motor Cortex
33	22, 43	Superior temporal gyrus, Primary gustatory cortex
43	21, 22	Middle temporal gyrus, Superior temporal gyrus Wernicke's area
44	38, 48, 21	Temporopolar area, Retrosubicular area, Middle temporal gyrus

4.3.3. Male vs. female differences

When an overall analysis was preformed on combined results from both studies, a substantialy and significantly higher MSSQ score was found in female participants when compared to males (25.8±4 vs.10.4±2.6, respectively, p=0.009, Fig. 9A). The second sex difference was significantly higher nausea rating in females compared to males just prior the termination of the ride (5.4±0.5 vs. 3±0.8, respectively, p=0.03, Fig. 9B). Finally, the tolerated ride duration was significantly shorter in females compared to males (7.0±0.7 vs. 10.9±1.4 min, respectively; p= 0.03, Fig. 9C). Analysis of physiological data such as HR, SAP, DAP, NIRS Hb-O_2 did not show any significant difference between female and male participants.

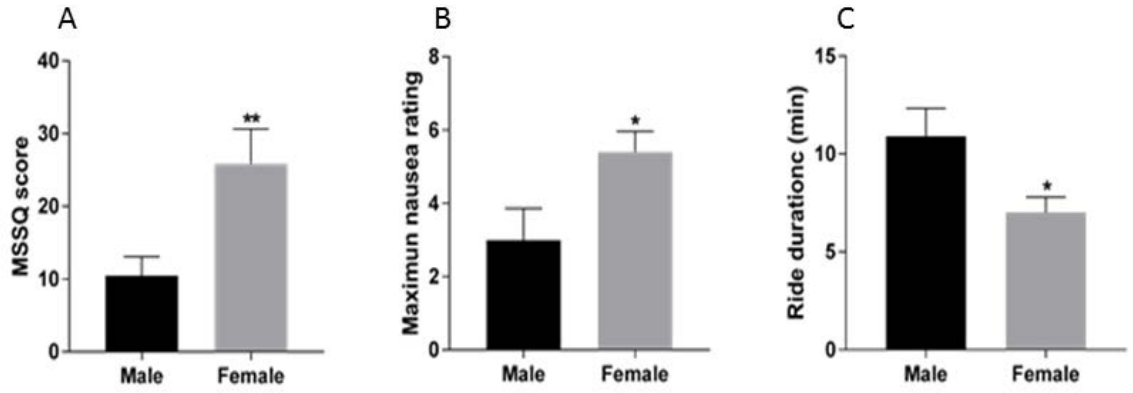

Fig. 9. Diffrences between male and female participants in MSSQ score (A), maximum nausea rating (B) and tolerated ride duration (C). * - $p<0.05$, ** - $p<0.01$

4.4. Discussion

The aim of the current study was to determine the effect of motion sickness on the brain blood flow during exposure to the provocative visual stimulation. In this regard, we used TCD ultrasonography to measure blood flow velocity in the two main cerebral arteries. Independent from the TCD setup, NIRS was used to monitor HbO_2 concentration during the same visual stimulation. In both experiments, nausea scores were recorded to monitor symptoms development. Of note, susceptibility and provocative effects of the virtual ride were very similar to those reported in our two previous studies where identical visual provocation was employed (31, 32).

This study provides two main findings. Firstly, we observed mild reduction in MCA and PCA conductance during motion sickness experience, suggesting vasoconstriction in downstream vascular beds supplied by the MCA and PCA in the TCD study. These changes were associated with mild increases in arterial pressure and heart rate. Importantly, the cardiovascular changes correlated with subjective nausea levels. Secondly, outcomes from the NIRS study showed apparent disaccord with the results in TCD study. When interpreting this discrepancy, in must be taken into account that the two methods assess different physiological variables – content of HbO_2 reflecting blood supply to the cortical region (NIRS); or blood velocity in the two major cerebral arteries (TCD). Still, it is hard to reconcile substantial increases in cortical blood flow in brain areas responsible for balance and vestibular inputs in subjects who experienced nausea and motion sickness symptoms with modest generalized decrease in cerebral blood flow

in the same individuals. In the following discussion, we focus on these findings separately, and then try to explain the controversy.

Our TCD findings are in a good accord with a previous study by Serrador et al. who also found a decrease in cerebral blood flow velocity suggesting brain hypoperfusion during provocative motion (human centrifuge) (7). Likewise, small but significant pressor responses were found in both experiments. These observations may suggest that reductions in cerebral blood flow are essential for the development of motion sickness. In the study by Serrador et al., the increase in cerebrovascular resistance has been linked to the auto-regulatory response aiming to sustain a constant cerebral blood flow when there is an alteration in BP. The authors suggested that increases in BP result in vasoconstriction to preserve a relatively constant cerebral blood flow. In the TCD study we also found small but significant increases in HR, systolic and diastolic arterial pressure after the onset of symptoms. These findings are consistent with our previous findings and other studies in this field (7, 31, 34). While identifying a precise origin for the fluctuations is difficult, one possible cause of the autonomic changes could be due the general excitement/arousal associated with the onset of the virtual ride. In fact, in our previous study (32) we concluded that the increase in heart rate introduced during VIMS cybersickness is mostly associated with anxiety rather than with motion sickness *per se* and found that exposure to VIMS caused a significant decrease in cardiac vagal tone, which was associated with anxiety. Increases in anxiety ratings during VIMS have also been reported by Farmer et.al in a recent study on 98 healthy individuals (34), where he reported increased sympathetic and decreased parasympathetic tone, respectively, using cardio-metric indices.

Numerous functional studies have documented that an increase in HbO_2 concentration has been linked with cortical activation in specific regions of the brain (22, 23, 35). Changes in cortical activity during motion sickness and nausea have been reported using functional magnetic source imaging (36), electroencephalography (37) and fMRI (38). In this study we used NIRS to monitor cortical activation during VIMS which has previously been shown to have close correspondence to fMRI signals with significant spatial and temporal correlations (28) (29). Analysis of the NIRS results show a significant increase in HbO_2 concentration in 15/52 channels of the NIRS device (Hitachi, ETG 4000). This increase in recorded HbO_2 concentration was correlated with increasing nausea and motion sickness symptoms (11/15 channels). According to a study by Sato et al. (21) investigating the correspondents of NIRS

channels and Broadman regions (39) the activated channels correspond to 9 cortical Broadman regions as shown in Table 1.

When considering the functional aspect of these cortical regions, many of them have been linked to motion sickness, nausea or in general to the vestibular sensory processing. One of the regions where a significant increase in HbO_2 concentration has been recorded is the inferior frontal gyrus; this area has been previously linked to visually induced motion sickness (34). The superior temporal gyrus (STG) and middle temporary gyrus (MTG), two other regions activated during VIMS, contain the primary auditory cortex, which is responsible for processing sounds, semantic control, and a region for processing multisensory integration. Previous studies have also linked inputs from a vestibular system origin to these regions (40, 41). STG has also been linked with active balancing (42, 43). Supra-marginal gyrus (SMG) was also activated in our study; this region located in the parietal lobe has been described in many studies as an important element for analysing vestibular inputs (41, 44, 45). The importance of the supra-marginal gyrus (SMG) has also been demonstrated by trans-cranial magnetic stimulation and fMRI to play a role in proprioception and resolution of conflicting sensory information such as sensorimotor conflicts (46, 47). SMG has also been shown to play an important role in balance and maintaining postural stability (42, 43).

The primary gustatory cortex (GC) was activated in both hemispheres (channels #20, #31, #33, #41), this structure is known for its role in perception of taste has also been linked to more general functions rather than working as the receptive field of peripheral taste receptor cells. The central gustatory pathways operates as a multisensory structure that is dedicated to assessing the significance of intra-oral stimuli. Among these functions is the ability of GC to combine taste information with the post-ingestive consequences that follow the consumption of food (48). Therefore one can argue that the activation of the GC region can be linked to the common symptoms of stomach awareness and nausea in motion sickness.

The supplementary motor area which is directly related with movement and balance was also activated during the VIMS test in this study. This activation potentially could be linked to the body movements associated with the ride.

Interestingly, only one subject was not affected by the motion sickness provocation during the NIRS recording. This subject reported no nausea or any other motion sickness related symptoms which was consistent with his MSSQ score of zero. The subject tolerated the

maximum duration of the ride and rated zero for motion sickness related symptoms. The NIRS results for this subject showed minimal or no activation of the aforementioned regions. This finding shows that the regions activated in subjects with motion sickness is not activated in the subject with no symptoms.

In summary, previous brain imaging studies reported changes in cortical activity during motion sickness (34, 36, 38, 49). Overall there is a good accord in locations of activated areas between these studies and our experiments. However, there are some inconsistency in the activated areas described by Farmer et al. (34) who noted negative correlations between intensity of nausea and neural activation in regions such as tonsil, lingual gyrus, posterior cingulate cortex and also a positive correlation with the inferior frontal gyrus. These findings are in contrast with the study by Napadow (38), and the discrepancies could be potentially explained by the differences in the experimental protocol and the subject selection, and further confirm the complexity of mechanisms involved in developing motion sickness.

The most challenging question of the current discussion is how to reconcile contradicting results obtained by the two different methods. As already noted, our TCD results are in good agreement with two previous studies using the same method. One limitation of TCD is that it measures cerebral blood velocity rather than flow. In order for velocity variations to correspond to flow changes, the diameter of the artery must remain constant. In a study combining MRI and TCD, Serrador et al. confirmed that MCA diameter at the intonation point does not change during large fluctuations in cerebral flow velocity provoked by changes in end tidal CO_2 and lower body negative pressure (50). So how can it be that a small global fall in cerebral blood flow is associated with regional cortical increases in HbO_2 concentration reflecting increases in local blood supply? The only possibility that we can propose to explain this puzzling observation is that with the development of nausea and other motion sickness symptoms, a complex re-balancing occurs in the brain hemodynamics, so that increases in blood supply in described cortical regions are potentially offset by decreases in deeper cortical and subcortical areas (such as hypothalamus, pons or medulla) that are not accessible to NIRS detection, and resulting in small global reduction in CBF. This alteration in blood flow results in increased perfusion in some critical regions responsible with balance (vestibular region) and deactivation of some other regions as described by Farmer et al. in his recent study using fMRI to image cortical activation during VIMS (34).

There was a substantial difference in susceptibility to cybersickness between the subjects. This was determined both by subjective and objective measures. Since one of our exclusion criteria was previous exposure to VR, these differences were clearly unrelated to this factor. However, it is not excluded that variations in symptoms were in part due to possible differences in head movements throughout the ride, and lack of considering this constraint is a study limitation. It is however implausible that the extent of head movements made a significant contribution to the sensory conflict, due to the very nature of the VR hardware and software that matched voluntary induced shifts in the virtual visual field due to head rotations and tilts, thus preventing vestibulo-visual sensory mismatch. Therefore the actual interaction was between virtual linear and angular accelerations and lack of corresponding sensations from the vestibular receptors which resulted in a vestibulo-visual conflict.

We found that sensitivity to cybersickness is higher in females compared to males. This result is in accord with findings from other studies with visually induced motion sickness (51-53). It is well established that females are also more sensitive to provocative motion stimuli (54, 55); combined, these facts suggest that sex-related mechanisms exert their action via affecting central processing of relevant information rather than influence initial sensory processing. We did not find expected sex differences in physiological changes associated with cybersickness; one potential reason for this is a relatively small number of participants in our pilot study. The major argument in favour of this idea is that sex differences for nausea sensitivity reached the level of significance only when data were analysed from all participants together, but was insignificance when the data were analysed separately for TCD and NIRS groups.

In conclusion, considering earlier studies (34), (36, 38, 56) together with our results, we conclude that motion sickness in general and nausea in particular is associated with variations in brain activity (region-specific increases and decreases) in a complex pattern in numerous cortical regions related to the cognitive evaluative and sensory discriminative aspects of this syndrome (49). The findings in this study can further emphasize the complexity of neural pathways during motion sickness and underline the importance of the vestibular system in developing motion sickness. Our results provide an incremental step towards resolving a fundamental question of identifying a neural substrate of motion sickness. From immediate practical perspective, our finding represent interest is in the field of occupational health rather than clinical settings. In a most recent pilot study we have confirmed that cortical flow is also

elevated by motion-induced motion sickness. The latter is a major problem during pilot training, and providing reliable biomarker of nausea will be of major benefit here.

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Chapter 5: A comparative study of cybersickness during exposure to virtual reality and "classic" motion sickness: are they different?

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Abstract

Existing evidence suggest that cybersickness may be clinically different from "classic", motion-induced sickness; this evidence was however obtained in separate studies that focussed on just one of the two conditions. Our aim was to bring clarity to this issue, by directly comparing subjective symptoms and physiological effects of motion sickness induced by physical motion (Coriolis cross-coupling) and by immersion in virtual reality (ride on a roller coaster) in the same subjects. A cohort of 30 young healthy volunteers was exposed to both stimulations in a counter-balance order on two separate days at least one week apart. Nausea scores were recorded during the exposure, and the Motion Sickness Assessment Questionnaire (MSAQ) was used to profile subjective symptoms post-experiment. Tonic and phasic forehead skin conductance level (SCL) was measured before and during exposure in both stimulation methods. We found that the nausea onset times were significantly correlated in both tests ($r=0.40$, $p=0.03$). Similarly, the maximum nausea ratings were significantly correlated during both provocations ($r=0.58$, $p=0.0012$). Symptom profiling with the MSAQ revealed substantial and significant correlations between total symptom scores ($r=0.69$, $p<0.0001$), between each of four symptom clusters and between 15/18 individual symptoms assessed in both conditions. Both virtual reality and Coriolis cross-coupling provocations caused an increase in tonic SCL associated with nausea (Mean Diff = 5.1, [2.59, 6.97], $p=0.007$ and Mean Diff = 1.49, [0.47 7.08], $p= 0.0001$, respectively), with a close correlation between the conditions ($r=0.48$, $p=0.04$). This was accompanied by a significant increase in the amplitude of phasic skin conductance transients in both visual stimulation and Coriolis cross-coupling when participants reported maximum nausea compared to no nausea (Mean Diff = 0.27, [0.091 0.63], $p <0.001$ and Mean Diff = 0.235, [0.053 0.851], $p<0.006$, respectively). We conclude that symptoms and physiological changes occurring during cybersickness and "classical" motion sickness are quite similar, at least during advanced stages of these malaises.

Keywords: motion sickness, cybersickness, virtual reality, nausea and skin conductance.

New and Noteworthy

Expansion of VR technology has provoked an interest in cybersickness – a subtype of motion sickness induced by immersion in VR. Finding means for preventing and managing cybersickness requires good understanding of its nature, including its relationship to "classical" motion sickness. The knowledge about this relationship is controversial, partly because there were no studies where the same cohort was exposed to the two provocations. Using this

approach, we demonstrate that symptoms and physiological manifestations of the two conditions are identical.

5.1. Introduction

Dominant symptoms of motions sickness (MS) are nausea and cold sweating. Careful clinical profiling has however revealed that MS has much broader, complex and diverse symptomatology. Previous studies have categorized MS symptoms into four main clusters: gastrointestinal (stomach awareness, nausea, vomiting); central (fainting, light-headedness, blurred vision, disorientation, dizziness, sensation of spinning); peripheral (sweating, feeling hot) and sopite (annoyance, drowsiness, tiredness, uneasiness) (1). The latter group of symptoms is less known; they may develop as a sole manifestation of MS or can be combined with other symptoms. Individual susceptibility to MS varies greatly and depends both on the scale of provocation and on individual factors such as sex, age and ethnic background (2).

Neural mechanisms responsible for MS are still poorly understood. Currently, the dominating "sensory mismatch" theory suggests that MS develops when conflicting signals are received from the spatial orientation senses - the vestibular system, the eyes and the non-vestibular proprioceptors (3-5). This conflict can be initiated by purely vestibular stimuli (eg. Coriolis cross-coupling leading to canal-otolith mismatch (6, 7)), by purely visual stimuli (eg. optokinetic drum leading to visual-vestibular mismatch (8-10)), or by combination of the two (as it happens in most instances of car- air- and seasickness). Vision on its own is not essential for MS since blind people are susceptible to it (11). On the other hand, subjects with bilateral vestibular deficit are immune not only to motion-induced MS but also to visually-induced MS (12). In this case, visual stimuli serve as a trigger for MS but the integrity of vestibular system is essential for its development. Earlier studies (13-16) have concluded that MS and nausea are associated with variations in brain activity (region-specific increases and decreases) in diverse regions such as the medial prefrontal cortex, ventromedial prefrontal cortex/pregenual cingulate cortex, anterior insula and mid-cingulate cortices (MCC) related to the cognitive and sensory components of this syndrome (17).

Cybersickness is a subtype of motion sickness that may accompany immersion in virtual reality (VR). While its first description was made decades ago (18), it is only recently that it gained the attention of academic researchers and industry developers. An explosion of consumer VR head-mounted displays (such as Oculus Rift, Samsung Gear VR or HTC Vive) that occurred

during the last several years was paralleled by dramatic increase in both mass media and research publications that confirmed the provocative liability of the technology (19, 20). According to the "sensory mismatch" theory, the most likely cause of cybersickness is a mismatch between visual stimuli and the appropriate vestibular or proprioceptive feedback. Additional factors contributing to motion sickness can be separated into either hardware dependent (sensor-induced delay, display flicker, frame rate) or content dependent (visual flow direction, presence of linear or angular accelerations) categories (21, 22). Still another distinct subtype of MS is simulator sickness; the bulk of research on this subject was performed in flight simulators, where participants received both visual and, to various extent, motion stimuli. It was reported that rotary-wing simulators had more provocative effects compared to fixed-wings ones (23).

One unresolved issue in the field of MS research is whether different subtypes of MS represent separate clinical entities. The answer to this question could be obtained by comparing subjective symptoms and physiological changes induced by different MS-provoking stimuli, and few such comparisons were indeed performed. For example, Kennedy al (23) reported that seasickness and simulator sickness differ in their symptom profiles, with nausea being a dominant symptom for the former and oculomotor disturbances – for the latter. In another publication (24) comparing several separate studies, the authors concluded that exposure to virtual environments can result in more severe symptoms than exposure to simulators, and while symptom profile differed between the two conditions, in neither case was nausea a dominant symptom. On the other hand, we found that the symptom profile of cybersickness was identical to that of "classical" motion-induced MS, with nausea having the highest score (25). This controversy motivated us to design and conduct the current study.

We propose and advocate the idea that in order to compare symptomatology of two (or more) related disorders, data should be collected from subjects who have progressed to a similar degree of symptom malaise/severity. In many instances (eg. respiratory viral infections), dominant symptoms during a prodromal stage are very different from dominant symptoms during disease culmination, and the same could be true for the group of MS disorders. We suggest that lack of control for this confounding factor might underlie the differences reported in the studies cited above. Another potential source of apparent differences is the inter-individual variability in sensitivity to MS-inducing stimuli. For instance, in one of the studies where cybersickness was reported to provoke greater severity compared to simulator sickness,

one of the limitations reported by the authors was the differences between their subjects (college students vs. military pilots in cybersickness and simulator sickness experiments, respectively) (24). With these considerations in mind, we aimed to compare symptom profiles of "classical" MS and cybersickness; to this end, we exposed our subjects to two well validated provocative stimuli – Coriolis cross-coupling (6, 7, 26) for the former and a virtual ride on a roller coaster (21, 25) for the latter. In order to control for MS severity, we asked subjects to continue exposure until it became too uncomfortable to tolerate. To exclude confounding effects of individual sensitivity, we used the same cohort of volunteers in both tests, in a counter-balanced manner. We also complemented subjective symptom scoring with a recording of forehead sweating – the most sensitive objective biomarker of MS (1, 24, 27).

An additional question that we intended to address in the current set of experiments is whether there is a correlation between the sensitivity to provocative motion and the sensitivity to provocative visual stimuli. If present, such dependence would allow using simple and relatively inexpensive VR technology for occupational pre-selection tests in those professions where motion sickness is an exclusion criterion or represents a common occupational hazard (eg. pilots, drivers of public transport, crane operators, etc.). It has been confirmed that those who score high on a retrospective motion sickness susceptibility questionnaires, are also more susceptible to provocative visual (28, 29) or vestibular intervention (30). However, to the best of our knowledge, there are limited studies (31) in the literature where sensitivity to provocative visual and vestibular stimulation was assessed in the same cohort, thus allowing direct comparison of the stimulation type. To this end, on different days we subjected our volunteers to a highly provocative VR or vestibular stimuli, and compared their subjective symptoms and physiological responses to these stimuli. Our two working hypotheses were: i) that both provocation methods will elicit similar symptom profiles; and ii) that sensitivity to one type of provocation will correlate with the sensitivity to the other.

5.2. Methods

5.2.1. Study participants

The study was conducted on 30 healthy volunteers (16 females and 14 males) aged 25.8±5.6 years. The study protocol was approved by the Human Research Ethics Committee of the Newcastle University. The volunteers were randomly allocated to two groups (n=15 each); on two different days (at least one week apart) the first group experienced a virtual ride on a

rollercoaster, while participants of the alternative group experienced vestibular stimuli (rotating chair, RC). The study was designed in a counter-balanced manner, so that participants from one group who experienced virtual ride on the first experimental day experienced rotating chair on the second day, while the order was opposite in the second group.

5.2.2. Experimental outline

On the day of arrival to the laboratory (air conditioned room), after signing an informed consent, subjects completed the Motion Sickness Susceptibility Questionnaire (MSSQ; (27)) and the Motion Sickness Assessment Questioner (MSAQ; (1)). The MSAQ was repeated after the test termination in each experiment day. In this questionnaire a list of common MS symptoms were presented to the participant. The symptoms were categorized in four clusters: gastrointestinal (nausea, feeling sick in the stomach, feeling queesy, about to vomit); central (faint-like, light headiness, disoriented, dizzy, and spinning); peripheral (sweaty, hot, clammy, cold sweat, temperature discomfort, need for fresh air); and sopite (annoyed, drowsy, tired, and uneasy). When answering each question of the MSAQ, the participant assigns a value from a range of 0 (“not at all”) to 9 (“severe”). These ratings were then summed for each group of related questions and used in a formula for each subscale, where Rating = (Sum of each subclass symptom rating)/[(number of the questions related to the corresponding subclass) × 8]. The overall MSAQ score was calculated as: Score = (Sum of all items / [(Number of all questions) × 8]; this results in a value between 0 and 4.

Forehead skin conductance was measured before and during the experiment using a wireless EquiVital life monitor (Hidalgo, UK) using self-adhesive surface electrodes. The electrodes were placed on the right and left sides of the forehead 1 cm bellow the hairline, at about the lateral corners of the eyes. The sensors were connected wirelessly by means of wi-fi dongle to a computer running Chart 8.0 (ADInstruments, Sydney, Australia). To compute the phasic component of the skin conductance signal, we applied a digital high-pass filter with a cut-off frequency of 0.05 Hz (6, 32). The amplitude (Root Mean Square, RMS) and frequency of SCL transients (phasic component) were calculated using LabChart software. A verbal rating of nausea was obtained from subjects every 30 seconds during the experiments. The nausea score ranged from zero (no effect) to 9 (just about to vomit).

5.2.3. Motion sickness provocations

In the Virtual reality experiment, after fitting the head-mounted VR display (Oculus Rift DK1, Oculus VR, USA), a 5-min baseline recording of forehead skin conductance was performed. During this period, a stereoscopic neutral static image was displayed on the rift monitor. Subsequently the VR rollercoaster simulation (Helix, Archivision, NL) was activated. The ride lasted for 15 min or until subjects felt uncomfortable and decided to terminate the ride, whichever came first. Subjects were asked to keep their heads as stable as possible during the ride. After ride termination the MSAQ was completed.

For the Coriolis cross-coupling provocation of MS, subjects were seated on the motorized chair (AB Stille-Werner, Sweden), with seatbelts fastened. A 5-min baseline recording of forehead skin conductance was performed while the subjects were seated with closed eyes. During the experiment, subjects were blindfolded and were asked to tilt their head as instructed by the operator. Commands for head tilts were given randomly in four directions: right, left, up and down, at a frequency of 16 tilts/min (6). Rotation commenced with a constant acceleration of $1^{\circ}sec^{-2}$ until a maximum speed of $200^{o}sec^{-1}$ was reached; subsequently the speed was kept constant for the rest of the study. The rotation lasted for 15 min or until subjects felt uncomfortable and decided to terminate the ride; this time included chair acceleration/deceleration. After the termination of rotation MSAQ was completed similar to the VR study.

5.2.4. Data analysis

Statistical analysis was performed using Prism v.7 (GraphPad, USA). Significance of the differences in nausea onset time, maximal nausea rating and in ride duration between the two conditions were assessed using paired t-tests. Significance of differences in MSAQ scores (total scores, individual symptom scores and symptom categories) were assessed using two-way ANOVAs for repeated measures followed by corrected multiple comparisons tests; independent variables were stimulation type (VR and RC) and time (pre- and post-test). Significance of differences in SCL parameters (tonic level, frequency and amplitude of transients) were assessed using two-way ANOVA for repeated measures followed by corrected multiple comparisons tests; independent variables were stimulation type (VR and RC) and nausea level. Sidak's method was used to correct the multiple comparisons tests. Prior to

performing correlational analysis, relevant data sets were checked for normality using D'Agostino & Pearson and Shapiro-Wilk tests. We then used Spearman correlation test for the data sets with non-Gaussian distribution, and Pearson's correlation for normally distributed data. Data are presented as means ± standard error of the mean (SEM). Statistical significance was set at $p<0.05$ with 95% confidence interval (CI).

5.3. Results

5.3.1. Nausea onset time

There was no difference in nausea onset time between VR and RC stimulations (62±10.3, 51±10.6, respectively $p = 0.57$). There was a moderate but statistically significant correlation in the nausea onset time between the two studies ($r = 0.40$, $p = 0.034$, Fig. 1). Only one participant was able to conclude both VR and RC tests.

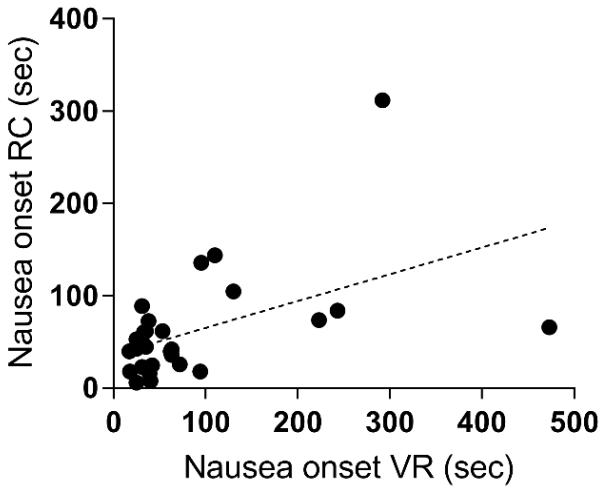

Fig. 1. Correlation between nausea onset times in RC and VR stimulation.

There was a weak but statistically significant negative correlation between the nausea onset time and the maximum nausea ratings in VR and RC studies ($r = -0.37$, $p = 0.048$ and $r = -0.42$, $p= 0.02$, respectively; Fig. 2A&B). Removal of outliers seen in Fig. 2B resulted in loss of significance. Interestingly, there was also a moderate negative correlation between the nausea onset time in the VR study and the maximal nausea rating in the RC study and vice versa: in other words, those who developed nausea earlier had higher maximal nausea rating not only in the same experiment but also in the other study ($r = -0.46$, $p = 0.009$ and $r = -0.39$, $p = 0.03$,

respectively, Fig. 2 C&D). Removal of obvious outliers seen in Fig. 2C and Fig. 2D resulted in change in the correlation coefficient in Fig. 2C (r= -0.39, p=0.031) and loss of significance in correlation in Fig. 2D (r= -0.33, p=0.071).

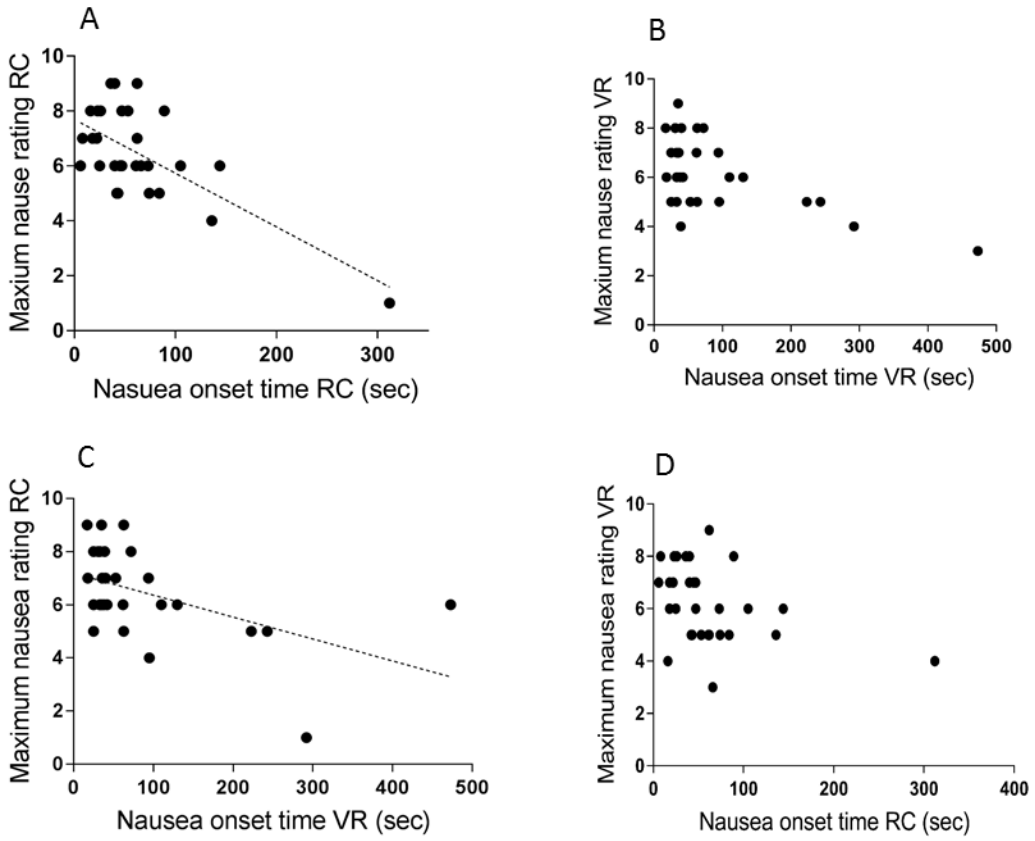

Fig. 2. Correlation of time of nausea onset in RC experiment and maximum nausea rating in RC (A), correlation of time of nausea onset in VR experiment and maximum nausea rating in VR (B), correlation of nausea onset time in VR and maximum nausea rating in RC (C), correlation of nausea onset in RC study and maximum nausea rating in VR.

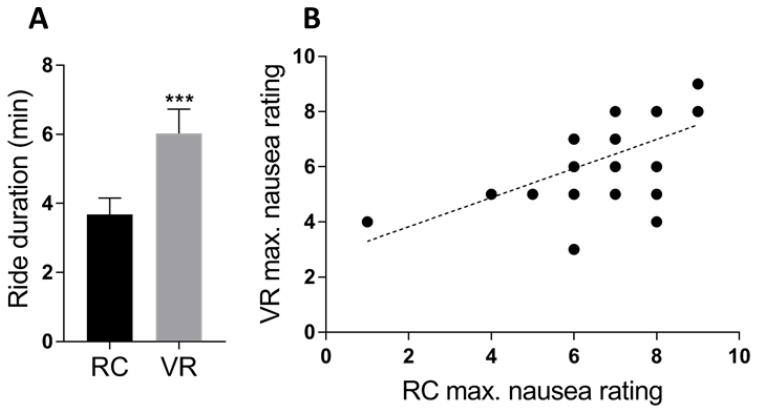

Fig. 3. Ride durations VR vs RC (A) and maximum subjective nausea rating in two conditions (B). Note that the data are shown for 30 participants, and apparent smaller number of points on the graph is due to overlap in several instances as scores were integer values.

5.3.2. MSSQ scores, tolerance time and nausea ratings during experiments

MSSQ scores varied greatly between participants; they ranged from 0 to 82.9 (mean = 26.6±21.0). All participants reported some level of nausea during both experiments. The majority of the participants (29/30) could not complete both VR and RC tests. The mean tolerance time was significantly longer in the VR ride compared to the RC test (3.6±0.4 min vs 6.0±0.6 min, respectively, $p<0.001$, Fig. 3A). There was no correlation between the tolerance-time between the two conditions. The mean values for the maximal nausea rating (i.e. the ratings at which participants requested to terminate the experiment) were 6.5±0.3 and 6.2±0.2 for RC and VR conditions, with no significant difference between them. Maximum nausea rating in VR experiment was significantly correlated with the maximum nausea ratings in the RC test ($r = 0.58$, $p = 0.001$) as illustrated in Fig. 3B.

5.3.3. Symptom scores by MSAQ

When assessed immediately after the experiments, two-way ANOVA analysis on the total symptom score showed no significant interaction between stimulation type and time ($p= 0.334$). The multiple comparison tests showed that the time factor did cause significant differences in both of the stimulations. Subjects reported significantly higher MSAQ total symptom scores following both the RC stimulation and the VR “ride”, when compared to

values reported before the experiment (Mean diff = -1.71, CI[-1.91,-1.5], p<0.0001 and Mean diff = -1.59, CI[-1.79,-1.39], p<0.0001 respectively, Fig. 4A). Total MSAQ scores were not significantly different when two stimulation methods were compared in the same time points.

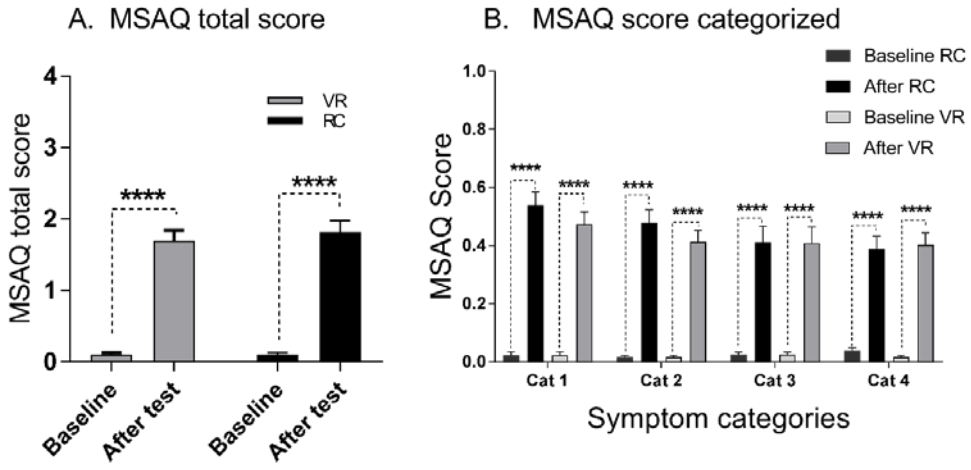

Fig. 4. Post-experiment symptoms evaluation. Total symptom score before and after VR and RC experiments (A), sub-categories symptom scores (B). ****, P<0.0001.

There was no significant interaction between stimulation type (RC vs. VR) and time (before vs. after) in scores of each category of symptoms (Cat1: p=0.091, Cat2: p=0.062, Cat3: p=0.901 and Cat4: p=0.33). However, multiple comparison tests revealed significant differences in category scores between two time points (before vs after) in both stimulation methods (Table 1). There were no significant differences in scores of each category in a single time (before vs after) when two stimulation type were compared.

Table 1. Baseline vs after test exposure MSAQ scores in each category of symptoms for RC and VR stimulation

Category of symptoms	***Stimulation***	***Mean difference, CI, p value***
Category 1: gastrointestinal	RC	-0.516, [-0.581,-0.451], p<0.0001
	VR	-0.451, [-0.515,-0.385], p<0.0001
Category 2: Central	RC	-0.461, [-0.517,-0.406], p<0.0001
	VR	-0.397, [-0.452,-0.342], p<0.0001
Category3: peripheral	RC	-0.386, [-0.459,-0.312], p<0.0001
	VR	-0.384, [-0.458,-0.311], p<0.0001
Category 4:	RC	-0.349, [-0.413,-0.284], p<0.0001
	VR	-0.387, [-0.451,-0.322], p<0.0001

The total post-experiment MSAQ scores obtained in both stimulations correlated substantially and highly significantly ($r=0.69$, $p<0.0001$; Fig. 5A and Table 2). Likewise, substantial and significant correlations were present between MSAQ sub-scores for each symptom category (Fig. 5B-E and Table 2). There was no significant difference between total scores or any the sub-scores mean values in both conditions.

Table 2. Mean post-exposure scores, their comparison and correlations for four motion sickness symptom clusters for virtual reality (VR) and rotation chair (RC) experiments.

	RC study (Mean±SEM)	VR study (Mean±SEM)	Mean difference	Correlation
Total MSAQ	1.60±0.04	1.81±0.04	NS	P<0.0001, r=0.69
Gastrointestinal	0.53±0.04	0.47±0.04	NS	P=0.0005, r=0.59
Central	0.47±0.04	0.41±0.03	NS	P<0.0001, r=0.69
Peripheral	0.41±0.04	0.40±0.05	NS	P<0.0001, r=0.67
Sopite	0.38 ±0.04	0.40±0.04	NS	P=0.001, r=0.54

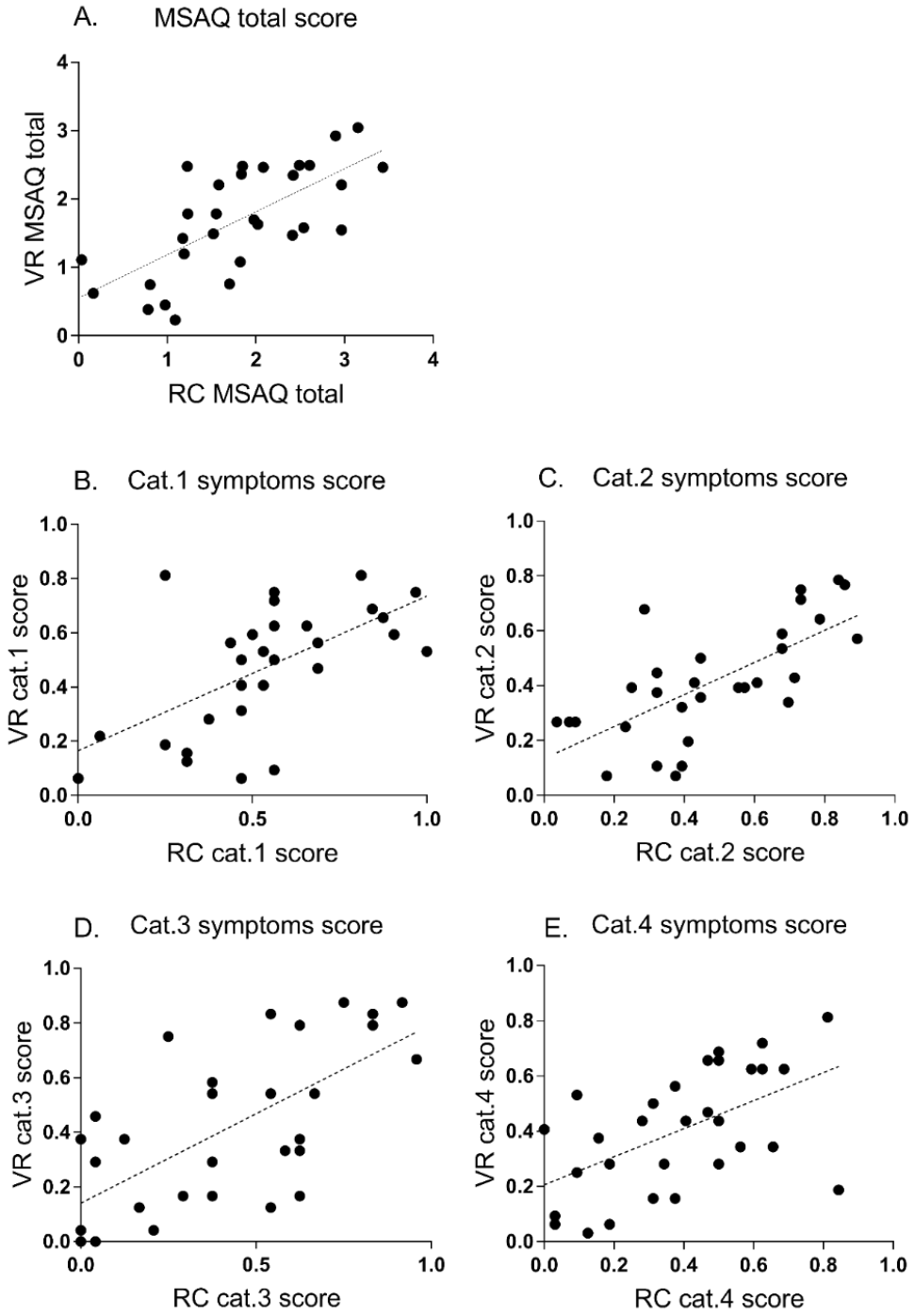

Fig. 5. Correlation of post-experiment symptoms in RC vs. VR conditions. A. Total MSAQ score; B. Category 1 (gastrointestinal); C. Category 2 (central); D. Category 3 (peripheral); E. Category 4 (sopite-like symptoms).

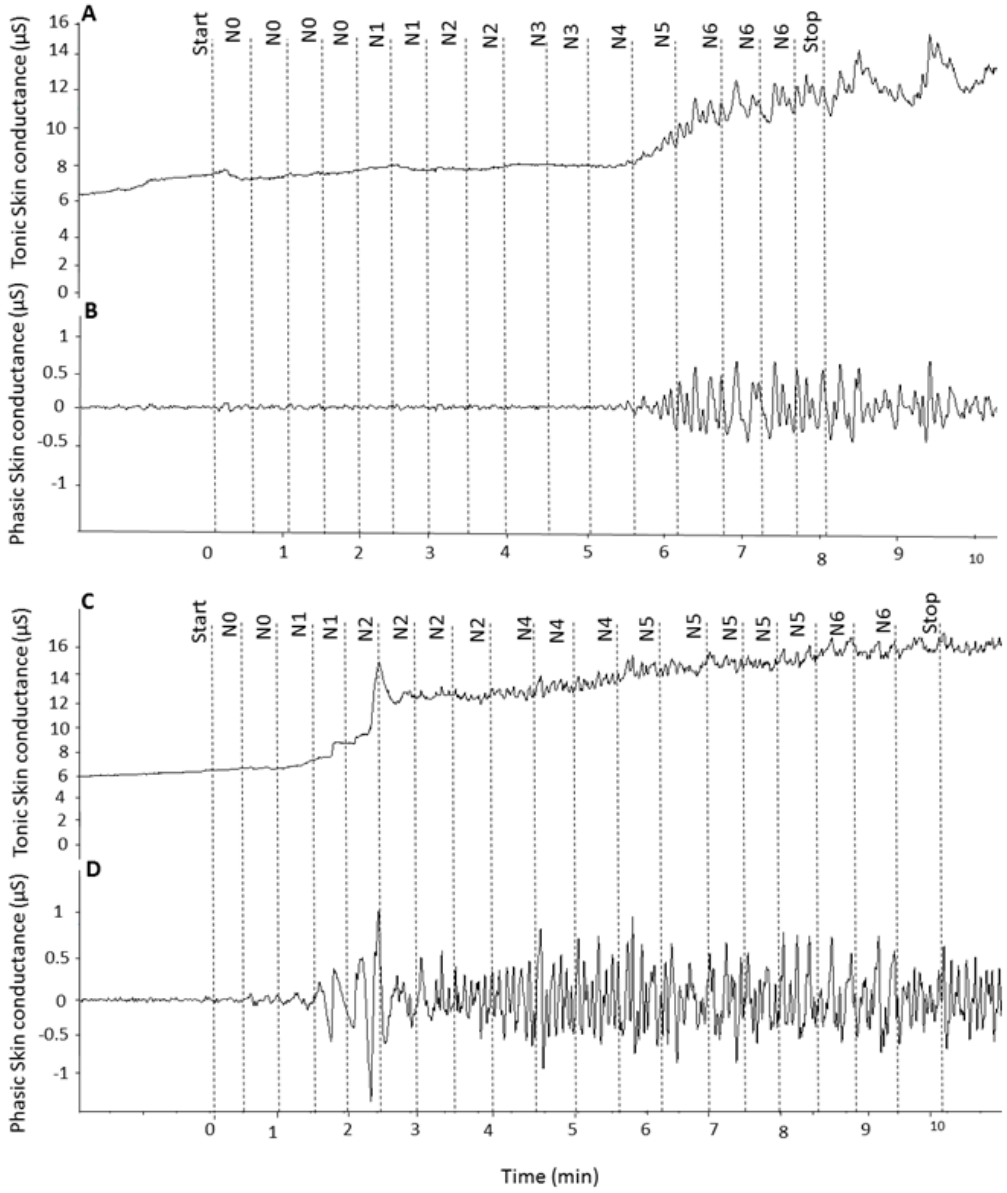

Fig. 6. An example of physiological recording during RC and VR experiments. Tonic skin conductance during RC stimulation (A), phasic skin conductance in RC stimulation (B), tonic skin conductance during VR stimulation (C), phasic skin conductance during VR stimulation.

Table 3 demonstrates individual symptoms reported by the participants after both studies. There was a significant correlation between both studies in all symptoms except 'feeling sick in the stomach'. The scores for 2/18 symptoms ('light-headedness' and 'annoyed') were weakly correlated and nearly significant ($r=0.31$, $p=0.088$ and $r=0.34$, $p=0.058$ respectively). The two-way ANOVA interaction results of stimulation type and nausea level (no nausea vs max nausea) was not significant in 15/18 of symptoms. Multiple comparisons tests showed no significant differences in symptom intensity at maximum nausea between the RC and VR

stimulation methods. However, there was a significant interaction between stimulation type and nausea level in 3/18 symptoms ('spinning', 'disorientation' and 'sensation of vomiting'; $p< 0.001$, $p< 0. 047$ and $p<0.041$, respectively). Grouped decomposition revealed that participants rated significantly higher in the RC study when compared to the VR study (Table 3).

Table 3. Mean MSAQ post-exposure scores, their comparison and correlations for individual motion sickness symptoms for virtual reality (VR) and rotation chair (RC) experiments.

Symptom clusters	Individual symptoms	Post-RC (Mean±SEM)	Post-VR (Mean±SEM)	Statistical difference	Correlation
Cat1: Gastrointestinal	Q1: Sick in the stomach	4.0±0.4	3.3±0.4	NS	No correlation
	Q5: Queasy	4.1±0.4	4.0±0.3	NS	r=0.59, p=0.0006
	Q11: Nausea	4.8±0.3	4.7±0.4	NS	r=0.69, p<0.0001
	Q15: About to Vomit	4.2±0.4	3.0±0.4	p=0.038	r=0.31, p=0.0892
Cat2: Central	Q2: Faint-Like	2.8±0.4	2.5±0.3	NS	r=0.36, p=0.0448
	Q6: Light Headiness	4.1±0.3	3.6±0.3	NS	r=0.31, p=0.088
	Q9: Disoriented	4.2±0.5	3.3±0.4	p=0.031	r=0.52, p=0.0029
	Q13: Dizzy	5.0±0.4	4.7±0.3	NS	r=0.61, p=0.0003
	Q14: Spinning	5.2±0.4	3.9±0.4	p=0.003	r=0.48, p=0.0068
Cat3: Peripheral	Q4: Sweaty	3.6±0.5	3.5±0.4	NS	r=0.68, p<0.0001
	Q12: Hot	2.7±0.4	3.2±0.4	NS	r=0.60, p=0.0004
	Q8: Clammy /Cold sweat	3.5±0.5	3.1±0.5	NS	r=0.63, p=0.0002
	Q18: Temperature discomfort	2.0±0.4	1.5±0.4	NS	r=0.51, p=0.0039
	Q17: Need for fresh air	3.4±0.5	3.4±0.5	NS	r=0.54, p=0.0020
Cat 4:Sopite	Q3: Annoyed	2.4±0.4	2.5±0.4	NS	r=0.34, p=0.0587
	Q7: Drowsy	3.0±0.4	3.0±0.4	NS	r=0.44, p=0.0149
	Q10: Tired	2.5±0.4	3.0±0.4	NS	r=0.46, p=0.0096
	Q16: Uneasy	4.4±0.4	4.3±0.4	NS	r=0.47, p=0.0075

5.3.4. Relations between nausea level and skin conductance

An example of the forehead skin conductance recordings (with nausea ratings) obtained in one subject during the VR and RC experiments conducted on different days are shown in Fig. 6. There was no difference in the tonic forehead SCL signal at baseline on any of the stimulation types, and no correlation between the two conditions (Fig. 6A&B). Two-way ANOVA results showed no significant interaction between stimulation type and nausea level in the tonic SCL ($p=0.35$). However, the onset of nausea was associated with elevation in tonic SCL In both VR and RC experiments, multiple comparisons test showed that the increasing trend of tonic SCL became significant at a time point associated with maximum subjective nausea in comparison to the SCL during baseline (Mean Diff. = 5.1, [2.59 6.97], $p=0.007$ and Mean Diff. = 1.49, [0.47 7.08], $p= 0.0001$, respectively, Fig. 7A). There was no significant difference between the stimulation types in a time points associated with "no nausea" or "max nausea" and correlation analysis showed significantly moderate correlation in the elevation of tonic skin conductance in both stimulation types ($r = 0.48$, $p = 0.04$, Fig. 7C).

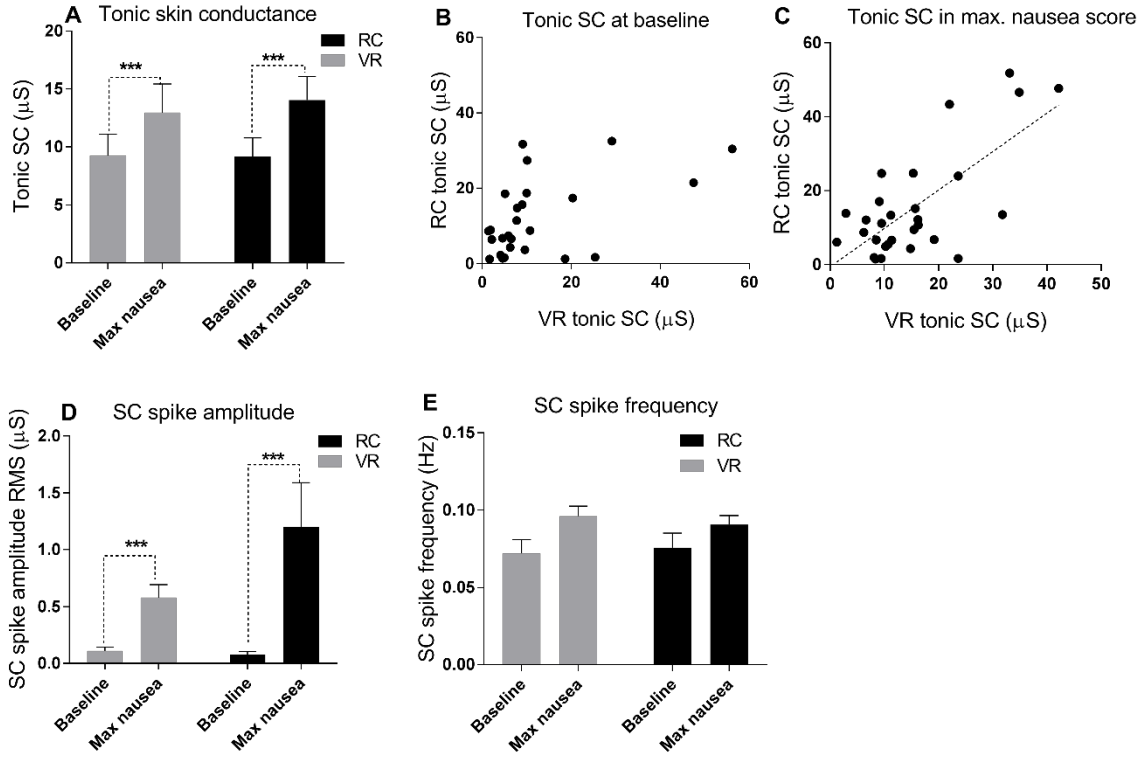

Fig. 7. Tonic and phasic skin conductance levels in maximum nausea rating and baseline. Tonic SCL(A), correlation of tonic SC level at baseline (B), correlation of tonic SC level at time point with maximum subjective nausea rating (C), Phasic spike amplitude RMS (D), Phasic event frequency (E).

There was minimal forehead phasic SC activity during baseline recording (Fig. 6 and 7D). Similar to tonic SCL the interaction of stimulation type and nausea level was not significant ($p=0.097$). The onset of MS symptoms was associated with an increase in the amplitude of the phasic skin conductance events; this elevation was substantial and significant at a time of maximal nausea rating, causing an increase in the root mean square values of the spikes in both VR and RC experiments when compared to baseline (Mean Diff = 0.27, [0.091 0.63], $p <0.001$ and Mean Diff. = 0.235, [0.053 0.851], $p<0.006$, respectively, Fig. 7D). There was no significant differences between the stimulation types in any time point associated with "no nausea" and "max nausea". While the frequency of the phasic SCL events tended to increase with increasing nausea ratings, this change did not become significant in either of the studies (Fig. 7E).

5.4. Discussion

The aim of this study was to compare subjective symptoms and physiological effects of motion sickness induced by physical motion and by immersion in virtual reality. For the former, we used a well characterized in the vestibular research and highly provocative stimulus – rotation around vertical axis with head tilts known as Coriolis cross-coupling stimulation (6, 7). For the latter, we used a version of a virtual ride on a roller coaster whose provocative potential we have proven in our previous experiments (21, 25, 28). To the best of our knowledge, this is the one of the first studies where the same participants were subjected to two classes of provocative stimuli, allowing direct comparison of sensitivity to these stimuli as well as comparison of symptoms and major physiological effects accompanying the two types of motion sickness. There are three main findings in this study. Firstly, sensitivity to both provocations (operationalized as latency to nausea onset) correlated between RC and VR studies. Secondly, both provocations resulted in the development of similar symptom profiles that closely correlated within individuals. Finally, we found that increases in forehead skin conductance paralleled progression of nausea in both condition.

5.4.1. Is there a relationship between sensitivity to vestibular and VR provocations?

Sensitivity to different aversive stimuli could be assessed in a number of ways, the simplest of which being a comparison of the time to the onset of an unpleasant sensation and the duration of time during which one could tolerate it. In our case, these measures are represented by latency to nausea onset and by ride tolerance time. It must be acknowledged that the nature of

our two stimuli was fundamentally different not only in their sensory modality but also in their progression. Specifically, VR "ride" started right from a "fall" from a rather high point, and prominent virtual accelerations – linear as well as angular - were present throughout the ride. In other words, while provocative potential of VR content varied from moment to moment, overall there was no gradual progression of this potential, in contrast to RC condition where head tilts became more and more provocative with increasing angular velocity of the chair (see Methods for the explanation of why this protocol was implemented). Because of this limitation, comparing absolute values of latency to nausea onset and of nausea tolerance time between the two conditions was not a valid approach. On the other hand, our correlational data for the latency to nausea onset indicate that those who were more sensitive to VR provocation were also more susceptible to vestibular stimuli. It must be acknowledged however that this correlation was weak to moderate. The weak to moderate correlations values can be attributed to the low power of the study caused by the limited number of participants in the study.

The maximal level of nausea induced by either provocation might serve as index of sensitivity to these stimuli only under the condition that they have similar duration; this was not the case in our study. The fact that maximal nausea levels correlated between VR and RC condition can be simply interpreted as an indication of similar subjective tolerance limits in both conditions for each subject. We did not find a correlation of ride tolerance time between the two conditions; this could mean either that there are no relationships between the two variables, or that it was obscured by the differences in temporal dynamics between the two provocations (as outlined in the previous paragraph).

Interestingly, the latency to nausea onset negatively correlated with the maximum nausea reported by the subjects in both experiments. In other words, subjects with shorter onset time reported a higher nausea rating at the end of the experiment, and tolerated a shorter duration of exposure. One possible explanation of this finding is that subjects who reported an early onset of nausea, continued to develop symptoms more rapidly as the experiment proceeded; on the other hand, individuals with a longer onset time developed symptoms slower and thus were able to tolerate longer exposure. Furthermore, we consider the finding of negative correlation between the nausea onset time in one study and maximum nausea rating in the other study of special interest, suggesting that subjects who experienced nausea in the early stages of a test reported higher nausea in both studies and vice versa. It must be acknowledged that these

correlations are weak to moderate; they nevertheless provide an indication that nausea onset time in one study could to some extent predict how a subject would feel in another study.

5.4.2 Is cybersickness a separate clinical entity?

Clarifying the question of whether cybersickness is clinically different from "classical", motion-induced motion sickness was one of our principal aims. For this purpose, we subjected the same cohort to visual and vestibular provocations and followed this by quantifying their symptoms using MSAQ, the most frequently used and well validated tool for assessment and profiling motion sickness (1). Similar to our previous work where virtual ride was the only provocative stimulus (21, 25), we found that the dominating symptoms in VR condition were the gastrointestinal ones, followed by central, peripheral and sopite-like symptoms (see Methods). Likewise, symptoms reported by our participants during RC provocation are in good accord with previous studies investigating motion sickness induced by provocative motion (1, 33, 34).

While comparing and analysing our MSAQ data, we targeted two specific questions: i) whether there were any differences in total MSAQ scores, in scores for the symptom clusters, or in the individual symptom scores between the two experimental conditions; and ii) whether there was a within-subject correlation for all these scores. Comparison of mean values for the total scores and for the cluster scores did not reveal any differences between the conditions, thus favouring the view that they represent essentially the same clinical entity. This was supported by substantial and highly significant correlations between the score pairs. Detailed comparison of individual symptom scores was generally in accord with findings for total and cluster scores: indeed, mean values did not differ for 15 out of 18 symptoms; of those, the highest correlation was found for feeling queasy or nauseous, dizzy, sweaty and hot. Of the remaining three (about to vomit, feeling spinning and disoriented), higher values were reported for RC stimulation. We propose that the difference in the sensation of "about to vomit" rating could be explained by the fact that the very termination of RC provocation (i.e. chair deceleration) was by itself an additional provocative factor. Indeed, whereas the action of VR provocation terminated immediately following subjects' request, chair deceleration must have induces an additional activation of vestibular receptors in semicircular canal, possibly resulting in stronger subjective sensation of near-vomiting. This same receptor activation triggered by a transition from a

rotation at constant angular velocity to angular deceleration also provokes a sensation of spinning that likely resulted in higher rating for this symptom in RC condition.

One potential confounding factor that might have affected our conclusions could be differing levels of severity of motion sickness between the two conditions. We argue here that in both instances, our participants reached reasonably similar levels of aversion – that is, the state when they felt too uncomfortable to continue the experiment. This is supported by similar maximal nausea ratings reported during the two provocations, and in the subsequent MSAQs. Overall, our analysis suggests that the clinical picture of advanced motion sickness (assessed as spectrum of symptoms and as their intensity) is very similar, independently of whether it is induced by pure visual or pure vestibular stimuli. This conclusion contradicts previously published results, and below we present our view on the potential causes of this controversy.

The principal sensory input responsible for provoking cybersickness is visual, and this places cybersickness close to simulator sickness that has been extensively studied (35, 36). While simulator sickness shares many common symptoms with "classic" motion sickness, some substantial differences have been reported between them. One the most influential paper on this subject (23) summarized several studies focused either on simulator sickness or on seasickness, and concluded that symptoms profile was substantially different. While during seasickness, the dominant symptom was nausea followed by oculomotor and disorientation, simulator sickness has the consistent pattern of "oculomotor > nausea > disorientation". Although some of the oculomotor symptoms (i.e. eyestrain) considered in the aforementioned study was not include in our questioners, the oculomotor symptoms investigated shows that nausea is a dominant symptom. We propose that the potential cause of this difference was possibly various degrees of severity of a condition: it is hard to imagine that if participants of simulator studies progress to near-vomiting, they still would rank nausea as less disturbing compared to oculomotor symptoms. We thus propose that the latter dominated at early stages of simulator sickness (especially when CRT computer monitors were used), and because exposure to provocative stimulation terminated prior to the tolerance limit, participants had relatively low nausea ratings. Broadly speaking, symptom profiles may vary greatly with a progression of a disease (eg. common cold starts from fatigue, but most disturbing symptoms at its peak are blocked nose and headache). As outlined on the previous paragraph, our participants terminated exposure at their individual tolerance limit, and we thus compared symptoms at as close a motion sickness severity as reasonably possible; we consider this to be

a strong methodological aspect of our study. On the other hand, it remains plausible that symptom profile may differ and depend on provocation type during earlier, non-advanced stages of MS; one way of clarifying this issue is by using a shortened form of the MSAQ.

Another methodological strength of this study is that the same cohort of volunteers were subjected to the two types of provocative stimuli. The importance of this factor is best illustrated by a work that compared symptom profiles and severity of MS induced by flight simulators to those induced by immersion in VR (24). Apart from differences in the profiles, comparison revealed that total symptom scores during cybersickness was about three time higher compared to simulator sickness. One factor that potentially accounted for this differences (and acknowledged by the authors) was different study populations – most male military aviators who were self-selected to be resistant to motion sickness in simulator studies, and non-preselected college student, with 50% females, in cybersickness studies. Our experimental design completely eliminated this factor and allowed most accurate comparison of symptoms obtained in both condition in the same individuals. Of note, despite relatively small sample size, our participants represented a very broad spectrum of MS susceptibility as was documented by their MSSQ scores.

We have limited our physiological measurements to forehead skin conductance. Among all reported autonomic and biochemical variables (with the exception of plasma vasopressin (37)), forehead sweating rate is by far the most sensitive and one of the most specific changes during motion sickness. Indeed, we (21, 25) and others have demonstrated only minor or moderate effects of motion sickness on heart and respiratory rate, arterial pressure, heart rate variability, body temperature or gastric myoelectric activity (38-40). In contrast, rise in sweating rate is quite dramatic as shown in the current study and as was demonstrated previously for both visually induced MS (10, 21, 25) and during motion provocation (6, 32, 41). Furthermore, forehead sweating correlates with subjective nausea rating ((6, 21, 25) and current study) whereas changes in other autonomic measures (finger skin conductance, heart and respiratory rate) could be associated with arousal provoked by the onset of real or virtual motion (25, 42), making it difficult to identify and measure the response component related to motion sickness. Overall, our results are in a good accord with the previous studies of MS evoked by different provocations, where sweating responses were prominent (6, 32). In all participants, there was either minimal or no SCL activity on the forehead during baseline; in contrast, there was a significant increase in SCL when nausea level was high. Consistently with similarity in

subjective symptoms, we did not find any differences in forehead sudomotor responses between the two provocations.

We have previously addressed the question of why motion sickness is associated with "thermoregulatory" forehead sweating (43), by expanding the Teaisman's hypothesis of the "toxic" origin of nausea during MS (44). Teaisman has proposed that the brain erroneously interprets a visual-vestibular sensory mismatch as a sign of intoxication, and nausea provides a mechanism of aversive conditioning to prevent future toxin ingestion. If this is correct, it would not be unreasonable to suggest that other protective responses might be triggered by the same stimuli. It has been shown in rodents that reducing body temperature during intoxication is an adaptive survival strategy (45), and we suggest that this could represent a key to understanding thermoregulatory disturbances during MS. Indeed, looking at MS from this perspective, it becomes apparent that it is in fact associated with a complex integrative response including physiological (sweating, cutaneous vasodilation; see (43) for review), b .behavioural (cold-seeking (46)) and cognitive (altered perception of ambient temperature (46)) components that eventually leads to a fall of body temperature in humans (47). Confirming this hypothesis, we have recently discovered that provocative motion also elicits profound hypothermic responses in rats, musk shrews (48, 49) and in mice (50); this hypothermia was preceded by prominent cutaneous vasodilation – a major heat loss mechanism in rodents that is homologous to sweating in humans.

5.5. Conclusions and Perspectives

We compared the sensitivity to and the effects of the two different motion sickness-inducing provocations; we conducted both studies in the same cohort, and collected a subjective ratings when participants were in a reasonably comparable severity state of sickness. Despite fundamental differences in provoking stimuli and, consequently, in sensory inputs responsible for development of motion sickness, it appears that symptoms and autonomic changes were similar during VR and vestibular stimulation. We thus conclude that cybersickness and "classic" motion sickness are clinically identical, at least in their advanced stages. Since the temporal progress of the symptoms was not investigated in this study, it remains possible that symptom spectrum differs during onset and early development of these malaises.

Sensitivity to vestibular provocations could be reduced by repetitive exposure to provocative motion; this forms the basis for motion sickness desensitization - a recognized intervention in

Air Forces pilot training programs (7, 26, 51). These programs are however time consuming (weeks) and require expensive equipment items. It is not fully known whether desensitization occurs in the vestibular sensors in the inner ear, in central vestibular pathways or at higher levels where visual and vestibular stimuli interact. There is a limited evidence in favour of the latter: two studies reported cross-desensitization, when repetitive exposure to optokinetic drum reduced susceptibility to seasickness (52, 53). There are also some literature that support changes in the relevant rodent brain structures during adaptation to various alterations in vestibular inputs (54) . Our finding of moderate correlation in sensitivity to visual and vestibular stimuli indirectly supports the possibility of cross-desensitization, as it is not unreasonable to suggest that reducing sensitivity to one type of provocation can result in reduction in susceptibility to another type. Another potential practical implication of our results is using VR technology for identification MS-susceptible individuals – an essential task for occupational health and safety in professions where MS represents a risk of safety hazard.

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Chapter 6: New and noteworthy findings.

6.1. New findings:

- ***Symptom profiling of cybersickness.*** Our research experiments targeted autonomic changes and subjective symptoms that accompany cybersickness. We found that during cybersickness, gastrointestinal symptoms dominate; this is followed by sopite, central, and peripheral clusters, thus yielding a conclusion that cybersickness can result in a multidimensional spectrum of symptoms. To the best of our knowledge, this is the one of the first detailed profiling of cybersickness symptomatology with a well-validated psychometric instrument, MSAQ.
- ***Post-exposure symptom progression in cybersickness.*** One of our major findings is that following visual provocation, the central and sopite-related symptoms persist for at least 3h, gastrointestinal – for 2, and peripheral – for 1 h. Some symptoms such as sweating dissipate more rapidly; on the other hand, other symptoms such as nausea and fatigue can have longer time span. Some of our participants reported nausea 10 hours after exposure. These findings further emphasize that provocative virtual environment can result in serious side symptoms, and therefore further investigation on how to avoid or reduce these symptoms must be considered.
- ***Females are more susceptible to cybersickness than males.*** We found that sensitivity to cybersickness is higher in females compared to males. Females scored higher nausea ratings and tolerated shorter exposure when compared to males. This result is in accord with findings from other studies with visually induced motion sickness, and with observations made in "classical", motion-induced motion sickness**.**
- ***Cybersickness intensity is a factor of visual content.*** Our findings clearly demonstrate that the direction of visual flow in virtual environment has a significant effect on the symptoms reported by the subjects and the physiological changes during cybersickness. Our results thus represent one the first report presenting evidence that moving forward in a motion-rich virtual context appears to be more provocative than moving backwards; this is reflected in both subjective and objective signs of cybersickness. We hypothesise that the underlying mechanism responsible for the additional provocative potential of the forward direction may involve induction of an anxiety-like state that

potentiates effects of sensory mismatch. This hypothesis is in line with the rich literature linking anxiety and motion sickness.

- ***Forehead sweating is a reliable biomarker of cybersickness.*** Our findings demonstrate that motion sickness and cybersickness share a complex integrative response including physiological (sweating, cutaneous vasodilation), behavioural (cold-seeking) and cognitive. Throughout our studies, subjective reporting were used in combination with numerous physiological parameters to assess cybersickness; our physiological parameters included heart rate, respiratory rate, finger skin conductance, forehead skin conductance, hart rate variability parameters RMSSD and SDRR, systolic and diastolic arterial pressure, MCA and PCA conductance and brain perfusion imaging. Out of all measured parameters, skin conductance level on the forehead appear to be an ideal physiological biomarker for cybersickness. These changes are robust, substantial and nausea-specific in contract to other effects that are likely mediated by arousal. Consequently, forehead sweating could now be considered as a reliable biomarker of cybersickness.
- ***Cybersickness and motion sickness have similar characteristics.*** Despite fundamental differences in the provoking stimuli and consequently in the sensory inputs responsible for development of sickness, it appears that symptoms and autonomic changes are similar during VR and vestibular stimulation. We thus conclude that cybersickness and "classic" motion sickness are clinically identical, at least in their advanced stages. Moreover, our correlational data from chapter 5 indicate that those who were more sensitive to VR provocation were also more susceptible to vestibular stimuli, suggesting that sensitivity to one could be predicted by the other.
- ***Nausea onset time is a good indicator of symptom progression.*** Our data demonstrates that subjects with shorter nausea onset time reported a higher nausea rating at the end of the experiment, and tolerated a shorter duration of exposure. Therefore, tolerance to motion sickness can be predicted by measuring nausea onset time at the start of the stimulation.
- ***Desensitization can be achieved with repetitive exposure.***One of our major findings is that, similar to motion-induced motion sickness, repetitive exposure to cybersickness provocative content can result in desensitization. Although there are studies that have focused on subjective measures to document habituation (1). To the best of our

knowledge this study is one of the first reporting to demonstrate (objectively and subjectively) that desensitization occurs during virtual reality-induced motion sickness.

- ***Brain hemodynamic change during cybersickness.*** We found that there are significant changes in brain hemodynamic during cyber sickness. In a novel approach we used NIRS and TCD to investigate brain activation regions during cybersickness. We found that alteration in blood flow results in increased perfusion in some critical regions responsible for balance (vestibular regions) and deactivation of some other regions.

6.2. Practical significance of our findings and conclusions.

With the fast expansion of VR technology in everyday life, it is essential to improve our understanding of the underlying side effects of this valuable technology in order to prevent unwanted symptoms and in some cases utilize these adverse side effects to our benefit. Cybersickness is a major draw-back to the VR industry and its applications. In this study we investigated its common symptoms and physiological responses. We aimed to better understand the physiological changes during and after experiencing cybersickness. We attempted to see how the content of virtual environment effects cybersickness and identify biomarkers that could be used to recognize sickness. We managed to find significant changes in blood flow in some regions of the brain during cybersickness. We also aimed to develop a better understanding of the relationship between cybersickness and classical motion sickness.

We found that cybersickness is a complex syndrome, and that its symptoms can significantly affect daily routine tasks for an extended period of time. We now recognise that this syndrome results in the development of not just common gastrointestinal symptoms but also significant physiological changes in crucial regions of the brain. Our findings show that these changes are similar to changes reported in previous studies investigating “classical”, motion-induced motion sickness. Interestingly, these similarities between cybersickness and traditional motion sickness is not just limited to the symptom progression and physiological changes; we now know that adaptation to both stimuli occurs during repetitive exposure.

The fact that desensitization develops in response to both vestibular- and visually-induced provocations raises an intriguing question about the possibility of cross-desensitisation. It is not unreasonable to suggest that reducing sensitivity to one type of provocation can result in reduction in susceptibility to another type. While existence of cross-desensitization requires

vigorous testing, it may be that virtual reality-based technology represents a simple and cost-effective way to reduce sensitivity to other types of nausea provocations.

Screening for elevated motion sickness susceptibility is another potential practical implication of our results. We know that MS can cause a serious safety hazard in some professions, therefore VR technology can be utilized for identification of MS-susceptible individuals.

6.3. Future perspectives

- ***Training programs**:* Motion sickness is a serious problem during training in student pilots. Expensive and lengthy desensitization programmes are still used to reduce their motion sickness sensitivity. Considering the findings of this research study, we propose to test whether repetitive exposure to VR would lead to reduced sensitivity to motion stimuli.
- ***Medical diagnostic tool:*** Motion sickness has been linked to many disorders such as migraine, Meniere's disease and other forms of vestibular dysfunctions (2, 3). A recent study by Golding et al. (1) concluded that increase in motion sickness susceptibility can be due to the onset of Meniere's disease. Other studies have found that motion sickness susceptibility is a reliable criterion in diagnosis of childhood migraine (4). Thus screening, detecting and monitoring motion sickness can be regarded as a reliable tool assisting physicians in diagnosis and treatment of illness. Considering the findings of this study, it does not seem unreasonable to suggest that VR induced cybersickness can be used as a relatively accessible and inexpensive tool either in screening or early diagnosis in vestibular patients.
- ***Medical diagnosis:*** Nausea is a common symptom in many illness and therapies such as chemotherapy. Currently subjective reporting is used to quantify nausea and no objective measures are available (5, 6). However, in some cases receiving a reliable subjective reporting is either not feasible (non-verbal infants, post-operative patients and patients in intensive care) or not consistent (young children who cannot distinguish nausea from pain). In progressed stages of illness vomiting can be an indicator of nausea, however vomiting predominantly arises in the later stages of sickness and in some cases it is not present at all. Also, in infants vomiting can be mistaken for common gastroesophageal refluxes (GER) or "Spitting Up". According to the findings in this

study, forehead sweating is a reliable biomarker of nausea during motion sickness; therefore it is possible to suggest that forehead sweating can be considered a potential indicator of nausea in other illnesses. However, further extensive research in this filed is required to establish a comprehensive link between nausea and forehead sweating in other illnesses.

6.4. Study limitations

- **Recruitment:**

  One of major limitation throughout the study was the difficulty of recruitment due to the adverse side effects of the investigation. This limitation resulted in decreased statistical power.

- **Equipment limitation:**

a) Subjects were asked to limit their movement during the visual induced motion sickness to limit vestibular input, however some movement was still present due to immersive aspect of the virtual environment.
b) The signal quality in Transcranial Doppler ultrasound was not consistent in all subjects.
c) Near infrared spectroscopy has a limited penetration depth and hence reflection of the infrared light, therefore we relied mostly on the mapping of Sato et al. to identify regions of activations.
d) The activation and termination of the VR stimulation and Coriolis cross-coupling were relatively different. While the VR stimulation and termination was quite sudden and the intensity was constant throughout the stimulation the rotating chair had more gradual start and finish.

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APPENDIX: Published articles and permissions to use the publications in this thesis

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Profiling subjective symptoms and autonomic changes associated with cybersickness

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ABSTRACT

Our aim was to expand knowledge of cybersickness – a subtype of motion sickness provoked by immersion into a moving computer-generated virtual reality. Fourteen healthy subjects experienced a 15-min roller-coaster ride presented via a head-mounted display (Oculus Rift), for 3 consecutive days. Heart rate, respiration, finger and forehead skin conductance were measured during the experiment; this was complemented by a subjective nausea rating during the ride and by Motion Sickness Assessment Questionnaire before, immediately after and then 1, 2 and 3 h post-ride. Physiological measurements were analysed in three dimensions: ride time, association with subjective nausea rating and experimental day. Forehead, and to a lesser extent finger phasic skin conductance activity showed a correlation with the reported nausea ratings, while alteration in other measured parameters were mostly related to autonomic arousal during the virtual ride onset. A significant habituation was observed in subjective symptom scores and in the duration of tolerated provocation. The latter increased from 7.0 ± 1.3 min on the first day to 12.0 ± 2.5 min on the third day ($p < 0.05$); this was associated with a reduced slope of nausea rise from 1.3 ± 0.3 units/min on the first to 0.7 ± 0.1 units/min on the third day ($p < 0.01$). Furthermore, habituation with repetitive exposure was also determined in the total symptom score post-ride: it fell from 1.6 ± 0.1 on the first day to 1.2 ± 0.1 on the third ($p < 0.001$). We conclude that phasic changes of skin conductance on the forehead could be used to objectively quantify nausea; and that repetitive exposure to provocative VR content results in habituation.

1. Introduction

It is currently well accepted that motion sickness (MS, or kinetosis) develops when conflicting signals are received from the spatial orientation senses – vestibular, visual and proprioceptive. Such sensory conflict can be initiated within a single sensory system such as canal-otolith interaction during Coriolis cross-coupling, or between two or more sensory systems such as visual/vestibular/proprioceptive interaction when on a boat in rough seas (Reason and Brand, 1975). MS could be provoked by a broad variety of causes, and it is according to these causes and also according to the predominant sensory influence that MS has been historically classified as sea-, air- or carsickness; simulator sickness; space sickness; and visually-induced motion sickness. The key role of the vestibular system in the pathogenesis of MS is evident from the fact that subjects with bilateral vestibular deficit are immune not only to vestibular but also to visual provocations (De Wit, 1953; Johnson et al., 1999; Money, 1970).

Cybersickness refers to MS induced by the immersion of stationary users in moving scenes using computer-generated virtual reality (VR), especially with the assistance of more immersive interfaces such as VR head-mounted displays. Although such VR devices have been around for decades (Jerald, 2016; Sutherland, 1968), due to their high cost and limited application there has been little research conducted in understanding the biological impact of these devices. With the increasing trend in the application of VR and computer games in everyday life, it becomes evident that cybersickness is the main obstacle in broad adoption and commercial expansion of VR technology, especially in fields like education and training. There are numerous factors of VR technology that could be responsible for these alterations; generally they could be classified into two categories: hardware-dependent (e.g. a lag between head move and visual field move, monitor flicker, disaccord between vergence and accommodation) and content-dependent (e.g. vigorous linear and/or angular accelerations) (Jerald, 2016). Information regarding potential effects of cybersickness on human physiology is limited, and expanding this area was our primary aim for this work.

Abbreviations: HR, heart rate; MS, motion sickness; MSAQ, motion sickness susceptibility questionnaire; MSAQ, motion sickness assessment questionnaire; VR, virtual reality.

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PLOS ONE

RESEARCH ARTICLE

Effects of visual flow direction on signs and symptoms of cybersickness

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Abstract

Our objective was to assess the influence of visual flow direction on physiological changes and symptoms elicited by cybersickness. Twelve healthy subjects (6 male and 6 female) were exposed to a 15-min virtual ride on a rollercoaster on two different days in a counterbalanced manner, such half of participants were facing forward during the first ride while another half was facing backward. Forehead skin conductance, heart rate and HRV parameters (SDRR, RMSSD) were collected as objective measures; subjective symptoms were assessed with the Motion Sickness Assessment Questionnaire immediately after exposure. We found that while nausea ratings at which participants terminated the experiment did not differ between forward/backward rides, the mean ride tolerance time was significantly longer during reverse ride compared to forward ride (6.1±0.4 vs 5.0±0.5 min, respectively, $p = 0.01$, $\eta^2 = 0.45$). Analysis of HRV parameters revealed significant reduction in both RMSSD ($p = 0.02$, $t = 2.62$, $\eta2 = 0.43$) and SDRR ($p = 0.01$, $t = 2.90$, $\eta2 = 0.45$) in the forward ride; no such changes were found in the backward ride. We also found that amplitude of phasic changes in forehead skin conductance increased significantly in both ride directions. This increase however was significantly lower ($p<0.05$) in backward ride when compared to the forward ride. When assessed immediately post-ride, subjects reported significantly lower ($p = 0.04$) subjective symptom intensity after the reverse ride compared to the forward ride. We conclude that the direction of visual flow has a significant effect on the symptoms reported by the subjects and on the physiological changes during cybersickness.

Introduction

Motion sickness (MS) develops when conflicting signals are received from the spatial orientation senses [1]. This could either be visual/vestibular/proprioceptive conflict such as when on a boat in a rough sea or can be initiated within a single sensory system such as canal-otolith interaction during Coriolis cross-coupling (rotation around vertical axis with head tilts) [1], or by purely visual stimuli such as optokinetic drum [2]. Apart from real motion, MS could be provoked by other means. Simulator sickness is frequently experienced by pilots who undergo simulator training [3, 4]. Cybersickness is a form of MS which is provoked by exposure to virtual reality. The principal symptoms of MS are well known and include cold sweating, facial

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Wed 9/01/2019 7:40 PM

To: Alireza Mazloumi Gavgani <Alireza.MazloumiGavgani@uon.edu.au>;

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Cybersickness-related changes in brain hemodynamics: A pilot study comparing transcranial Doppler and near-infrared spectroscopy assessments during a virtual ride on a roller coaster

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ABSTRACT

Our aim was to assess cerebral blood flow changes during cybersickness. Transcranial Doppler (TCD) ultrasound and near-infrared spectroscopy (NIRS) were used separately in two independent experiments. In both studies, a 15-min virtual roller coaster ride was used as a provocative visual stimulus. Subjective nausea ratings were obtained at 1 min intervals. The TCD study was performed in 14 healthy subjects (8 males and 6 females); in this study we also measured heart rate and arterial pressure. In a separate study a 52-channel NIRS device (Hitachi ETG-4000) was used to monitor activated brain regions by measuring oxy-hemoglobin (HbO_2) concentration in 9 healthy subjects (4 male, 5 female). The TCD study results showed a significant increase in systolic (+3.8 ± 1.8 mm Hg) and diastolic (+6.7 ± 1.3 mm Hg) pressure at the end of the virtual ride (maximum nausea) compared to baseline (no nausea). We also found that middle cerebral artery (MCA) and posterior cerebral artery (PCA) systolic flow velocity decreased significantly at the end of the ride when compared to baseline values. Likewise, the relative systolic and diastolic conductance in the MCA decreased significantly ($-0.03 \pm 0.02\,cm \times s^{-1} \times mm\,Hg^{-1}$, t, $p = 0.0026$ and $-0.03 \pm 0.01\,cm \times s^{-1} \times mm\,Hg^{-1}$, $p = 0.05$, respectively) at maximum nausea when compared to no nausea. Additionally, there was a significant decrease ($-0.02 \pm 0.01\,cm \times s^{-1} \times mm\,Hg^{-1}$, $p = 0.03$) in the relative systolic conductance in the PCA at the end of the ride. Analysis of the NIRS results showed a significant increase in HbO_2 concentration in 15/52 channels in parieto-temporal regions of both hemispheres in participants who experienced motion sickness symptoms during the experiment. This increase in HbO_2 concentration correlated with increasing nausea and motion sickness symptoms. We conclude that cybersickness causes complex changes in cerebral blood flow, with an increase in perfusion in some cortical regions, but with a decrease of global cerebral perfusion.

1. Introduction

Motion sickness (MS) is considered to be a general feeling of discomfort in ordinary routine life but also a major operational hazard for pilots and space agencies. It is currently well accepted that conflicting signals from the spatial orientation senses – visual, vestibular and proprioceptive leads to the development of motion sickness [1]. This sensory conflict which was first described by Irwin [2] and later explained by James [3] in the early 19th century can be a result of single sensory system mismatch such as canal-otolith interaction during Coriolis cross-coupling, or between two or more sensory systems such as visual/vestibular/proprioceptive interference [4]. These early findings suggest that the vestibular system plays a critical role in the pathogenesis of motion sickness [2]. Other research has concluded that subjects with bilateral vestibular deficit are immune to motion sickness [3,5]; hence the vestibular system is indispensable in evolution of motion sickness. One potential cause of neuronal dysfunction responsible for motion sickness is alteration in regional cerebral blood supply; thus a close investigation of vestibular inputs in the regulation of cerebral blood flow is essential for better understanding the underlying mechanisms associated with motion sickness.

A recent study has found that people who suffer from motion sickness during parabolic flight are more likely to have orthostatic intolerance and increased cerebrovascular resistance after flight [6].

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RESEARCH ARTICLE

A comparative study of cybersickness during exposure to virtual reality and "classic" motion sickness: are they different?

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Mazloumi Gavgani A, Walker FR, Hodgson DM, Nalivaiko E. A comparative study of cybersickness during exposure to virtual reality and "classic" motion sickness: are they different? *J Appl Physiol* 125: 1670–1680, 2018. First published October 4, 2018; doi:10.1152/japplphysiol.00338.2018.—Existing evidence suggests that cybersickness may be clinically different from "classic," motion-induced sickness; this evidence was, however, obtained in separate studies that focused on just one of the two conditions. Our aim was to bring clarity to this issue by directly comparing subjective symptoms and physiological effects of motion sickness induced by physical motion (Coriolis cross-coupling) and by immersion in virtual reality (ride on a roller coaster) in the same subjects. A cohort of 30 young, healthy volunteers was exposed to both stimulations in a counterbalanced order on 2 separate days ≥1 wk apart. Nausea scores were recorded during the exposure, and the Motion Sickness Assessment Questionnaire (MSAQ) was used to profile subjective symptoms postexperiment. Tonic and phasic forehead skin conductance level (SCL) was measured before and during exposure in both stimulation methods. We found that the nausea onset times were significantly correlated in both tests ($r = 0.40$, $P = 0.03$). Similarly, the maximum nausea ratings were significantly correlated during both provocations ($r = 0.58$, $P = 0.0012$). Symptom-profiling with the MSAQ revealed substantial and significant correlations between total symptom scores ($r = 0.69$, $P < 0.0001$) between each of 4 symptom clusters and between 15/18 individual symptoms assessed in both conditions. Both virtual reality and Coriolis cross-coupling provocations caused an increase in tonic SCL associated with nausea [mean difference (mean diff) = 5.1, confidence interval (CI) = (2.59, 6.97), $P = 0.007$ and mean diff = 1.49, CI = (0.47, 7.08), $P = 0.0001$, respectively], with a close correlation between the conditions ($r = 0.48$, $P = 0.04$). This was accompanied by a significant increase in the amplitude of phasic skin conductance transients in both visual stimulation and Coriolis cross-coupling when participants reported maximum nausea compared with no nausea [mean diff = 0.27, CI = (0.091, 0.63), $P < 0.001$ and mean diff = 0.235, CI = (0.053, 0.851), $P < 0.006$, respectively]. We conclude that symptoms and physiological changes occurring during cybersickness and classic motion sickness are quite similar, at least during advanced stages of these malaises.

NEW & NOTEWORTHY Expansion of virtual reality (VR) technology has provoked an interest in cybersickness, a subtype of motion sickness induced by immersion in VR. Finding means for preventing and managing cybersickness requires good understanding of its nature, including its relationship to "classic" motion sickness. The knowledge about this relationship is controversial, partly because there were no studies where the same cohort was exposed to the two provocations. With this approach, we demonstrate that symptoms and physiological manifestations of the two conditions are identical.

cybersickness; motion sickness; nausea; skin conductance; virtual reality

INTRODUCTION

Dominant symptoms of motions sickness (MS) are nausea and cold sweating. Careful clinical profiling has, however, revealed that MS has much broader, complex, and diverse symptomatology. Previous studies have categorized MS symptoms into four main clusters: gastrointestinal (stomach awareness, nausea, vomiting), central (fainting, lightheadedness, blurred vision, disorientation, dizziness, sensation of spinning), peripheral (sweating, feeling hot), and sopite (annoyance, drowsiness, tiredness, uneasiness; Ref. 11). The latter group of symptoms is less known; they may develop as a sole manifestation of MS or can be combined with other symptoms. Individual susceptibility to MS varies greatly and depends both on the scale of provocation and on individual factors such as sex, age, and ethnic background (15).

Neural mechanisms responsible for MS are still poorly understood. Currently, the dominating "sensory-mismatch" theory suggests that MS develops when conflicting signals are received from the spatial orientation senses: the vestibular system, the eyes, and the nonvestibular proprioceptors (2, 3, 38). This conflict can be initiated by purely vestibular stimuli (e.g., Coriolis cross-coupling leading to canal-otolith mismatch; Refs. 4, 13), by purely visual stimuli (e.g., optokinetic drum leading to visual-vestibular mismatch; Refs. 18, 25, 50), or by combination of the two (as it happens in most instances of car-, air-, and seasickness). Vision on its own is not essential for MS since blind people are susceptible to it (17). On the other hand, subjects with bilateral vestibular deficit are immune not only to motion-induced MS, but also to visually induced MS (19). In this case, visual stimuli serve as a trigger for MS, but the integrity of the vestibular system is essential for its development. Earlier studies (23, 29, 34, 46) have concluded that MS and nausea are associated with variations in brain activity (region-specific increases and decreases) in diverse regions such as the medial prefrontal cortex, the ventromedial prefrontal cortex/pregenual cingulate cortex, and the anterior insula and the midcingulate cortices related to the cognitive and sensory components of this syndrome (42).

Cybersickness is a subtype of motion sickness that may accompany immersion in virtual reality (VR). Although its first

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