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## **Profiling subjective symptoms and autonomic changes associated with cybersickness.**

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

## 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  $7.0 \pm 1.3$  min on the first day to  $12.0 \pm 2.5$  min on the third day ( $p < 0.05$ ); this was associated with a reduced slope of nausea rise from  $1.3 \pm 0.3$  units/min on the first to  $0.7 \pm 0.1$  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  $1.6 \pm 0.1$  on the first day to  $1.2 \pm 0.1$  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.

## 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 et al., 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

The most common and known symptoms of MS are cold sweating, nausea and vomiting, and facial pallor (Money, 1970; Reason et al., 1975); 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) (Gianaros et al., 2001). A common established psychometric tool for their assessment is Motion Sickness Assessment Questionnaire (MSAQ) (Gianaros et al., 2001). 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 (Kennedy et al., 1993). 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 (Golding, 1992; Golding et al., 1997). 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. (Bagshaw et al., 1985; Lucertini et al., 2004)). 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. METHODS

### 2.1. *Participants and general experiment outline.*

The study was conducted in 14 healthy volunteers (average age  $29 \pm 6.1$  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) (Golding, 1998); 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) (Gianaros et al., 2001); 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  $\text{Rating} = (\text{Sum of each subclass symptom rating}) / [(\text{number of the questions related to the corresponding subclass}) \times 9]$ . The overall MSAQ motion sickness score is calculated as:  $\text{Score} = (\text{Sum of all items} / [(\text{Number of all questions}) \times 9])$ . 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. *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 (Golding, 1992; Golding et al., 1997). 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 =  $m \times \text{Time} + c$ ), 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 (Golding, 1992), 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<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>) 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  $\pm$  standard error of the mean (SEM). Statistical significance was set at  $p < .05$ .

### 3. RESULTS

#### 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,  $0.6 \pm 0.3$  for 1<sup>st</sup> min of the ride and  $5.3 \pm 0.4$  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 ( $F(2, 22) = 4.787$ ,  $p = .0188$ ,  $\eta^2 = 0.12$ ) 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<sup>rd</sup> day compared to the first two days ( $1.3 \pm 0.26$ ,  $1.3 \pm 0.20$  and  $0.7 \pm 0.1$  units/min, respectively;  $F(2, 24) = 6.4$ ,  $p = .0059$ ,  $\eta^2 = 0.13$ , 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 ( $17 \pm 15$ ). 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.

### 3.2. Immediate and delayed subjective symptoms induced by virtual ride.

Two-way ANOVA revealed significant effects of both “time of ride” ( $F(4, 44) = 24.78, p < .0001$ ), and “day” ( $F(2, 22) = 4.18, p = .03$ ) factors. Before the ride, mean MSAQ symptoms score was  $0.03 \pm 0.01$ ; 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 1<sup>st</sup> 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.

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).

### 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 ( $+9.3 \pm 2.1$  bpm) ( $F(2, 26) = 7.418, p = .0028, \eta^2 = 0.08$ ) 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 ( $F(2, 26) = 4.702, p = .0181$ ) but became non-significant on the Day 3 ( $+3.5 \pm 1.5$  and  $+4.2 \pm 1.8$  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 1<sup>st</sup> day, ride onset was associated with a small but significant tachypnoea ( $+2.2 \pm 0.6$  cpm) that gradually dissipated towards the end of the ride (Figs. 4, 5B and Table 2). This initial tachypnoeic response remained unchanged on the 2<sup>nd</sup> day ( $+2.8 \pm 0.7, F(2, 26) = 5.222, p = .0195$ ) and became non-significant on the 3<sup>rd</sup> day, ( $F(2, 24) = 1.676, p = .2082, \eta^2 = 0.04$ ).

### 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 1<sup>st</sup> min of the ride on the 1<sup>st</sup> day it raised by  $+9.2 \pm 2.5 \mu S$  ( $F(2, 26) = 19.01, p < .0001, \eta^2 = 0.392$ ) indicating increasing sweating in the finger; this response further increased towards the end of the ride (Fig. 4 and 5C). The initial (1<sup>st</sup> minute of the ride) increase in tonic finger SCL showed a decreasing trend on the 2<sup>nd</sup> and 3<sup>rd</sup> day ( $+5.5 \pm 1.3$  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 ( $F(2, 26) = 4.73, p=.0185, \eta^2=0.07$ ) and in RMS levels ( $F(2, 26) = 7.888, p=.0023, \eta^2=0.27$ ), of the forehead SCL signal between the baseline and the last minute of the ride (Figs. 5G and 5H); these differences persisted during the 2<sup>nd</sup> and 3<sup>rd</sup> days (Table 2).

### 3.5. Relations between nausea level and autonomic parameters.

On the 1<sup>st</sup> day, there was a small but significant increase ( $F(3, 56) = 2.808, p=.048, \eta^2=0.30$ ) 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 2<sup>nd</sup> and 3<sup>rd</sup> 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 1<sup>st</sup> day, finger tonic SCL significantly and substantially ( $F(3, 62) = 14.63, p<.0001, \eta^2=0.41$ ) increased during nausea experience, and this increase correlated with nausea levels (Fig. 6C). This increase at all levels of nausea was preserved on the 2<sup>nd</sup> and the 3<sup>rd</sup> 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 ( $F(3, 60)=2.626, p<.05, \eta^2=0.11$ ) different for nausea levels >3 (Fig. 6G), and this difference persisted during 2<sup>nd</sup> but not the 3<sup>rd</sup> day. Finally, the greatest changes were observed in the frequency of the phasic forehead SCL events that increased substantially and significantly ( $F(3, 62)=10.68, p<.0001, \eta^2=0.34$ ) at all levels of nausea on all three days (Fig. 6H and Table 3).

## 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 (Jerald, 2016) 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 (Golding, 1992; Golding, 1998). The subsequent discussion is focused on subjective symptoms of cybersickness and their habituation and on the finger-forehead differences of sudomotor responses.

#### *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 (Classen et al., 2011; Kennedy et al., 1993). 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, Kennedy et al. (1993) 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 (Kennedy et al., 1993; Kiniorski et al., 2004; Muth et al., 1996) 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 (Kennedy et al., 1993).

There is very limited research on the aftereffects of VR exposure. Using posturography, Cobb (1999) reported that immersion in VR produced mild and short-lasting postural instability. Another study (Stanney et al., 1999) 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.

#### *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 psychophysiologicals, and it is well established and accepted that a rise in finger SCL reflects increased arousal (Christie, 1973; Wilcott, 1967). Likewise, tachycardia and tachypnoea are common manifestations of stress/arousal (Arnold, 1945; Bloch et al., 1991; Boiten et al., 1994; Wolf, 1970). 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 3<sup>rd</sup> 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. (McClure et al., 1972) 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 (McClure et al., 1972). 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 (Golding, 1992; Golding et al., 1997) whereas cardiac, respiratory or pressor changes were either minor or absent (see (Stern et al., 2011) 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 (Golding, 1992; Golding et al., 1997) 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 (LaCount et al., 2011; Sclocco et al., 2016); 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 (Sclocco et al., 2016).

Supporting other studies of cybersickness (Kim et al., 2005), 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 (Golding, 1992; Golding et al., 1997; LaCount et al., 2011; Sclocco et al., 2016), 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 (Nalivaiko et al., 2014). In brief, we expanded Teisman’s idea of the “toxic” origin of nausea during MS (Treisman, 1977); 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 (Romanovsky et al., 1997). 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 (Nalivaiko et al., 2014) for review), behavioural (cold-seeking (Nobel et al., 2012)) and cognitive (altered perception of ambient temperature (Nobel et al., 2012)) components that eventually leads to fall in body temperature (Nobel et al., 2006). Confirming this hypothesis, we have recently discovered that provocative motion also elicits profound hypothermic responses in rats and musk shrews (Ngampramuan et al., 2013) 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.

#### *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 (Bagshaw et al., 1985; Lucertini et al., 2004). 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 of 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 (Farmer et al., 2015; Napadow et al., 2013; Sclocco et al., 2016). An indirect argument in favour of the latter suggestion is that sensitivity to motion predicts sensitivity to visual provocation (current study and (Nalivaiko et al., 2015)). Furthermore, there is a limited evidence of cross-desensitization, where repetitive sessions of optokinetic drum provocation resulted in prolonged reduction of susceptibility to seasickness (Ressiot et al., 2013).

#### *4.4. 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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**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.

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

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”; <sup>X</sup>, <sup>XX</sup> and <sup>XXX</sup> –  $p < 0.05$ ,  $p < 0.01$  and  $p < 0.001$ , respectively, compared to “Hour 1”; <sup>Y</sup> and <sup>YYY</sup> –  $p < 0.05$  and  $p < 0.001$ , respectively, compared to Day 1.

**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
<b>Heart rate:</b> ( $p=0.001$ 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	83.77 84±4
<b>Resp. rate</b> $p=0.037$ 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
<b>Finger tonic</b> $p<0.0001$ 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 ****####
<b>Finger RMS:</b> 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
<b>Finger Frequency:</b> 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
<b>Forehead tonic:</b> 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
<b>Forehead RMS:</b> $p=0.0001$ 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***##
<b>Forehead Frequency:</b> $p=0.0008$ 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 1<sup>st</sup> min of the ride.

**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
<b>HR:</b> $p=0.03$ 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
<b>Respiratory Rate:</b> 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
<b>Finger tonic:</b> $p<0.0001$ 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**** <sup>X</sup>
<b>Finger RMS:</b> 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 <sup>X</sup>	0.027±0.004	0.039±0.014
Day 3	0.019±0.009	0.061±0.013	0.076±0.018 <sup>Y</sup>	0.040±0.012
<b>Finger Frequency:</b> 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 <sup>X</sup>	0.097±0.009 <sup>XXX</sup>	0.086±0.021 <sup>XX</sup>
Day 3	0.096±0.020	0.109±0.010 <sup>XX</sup>	0.140±0.017	0.155±0.033
<b>Forehead tonic:</b> 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
<b>Forehead RMS:</b> $p=0.007$ 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 <sup>X</sup>	0.009±0.004 <sup>XX</sup>	0.020±0.006
<b>Forehead Frequency:</b> $p<0.0001$ 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** <sup>#</sup>	0.123±0.007** <sup>##</sup>
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; <sup>X</sup>, <sup>XX</sup> and <sup>XXX</sup> –  $p<0.05$ ,  $p<0.01$  and  $p<0.001$ , respectively, compared to Day 1; <sup>Y</sup> –  $p<0.05$  compared to Day 2.compared to Day 2.

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## FIGURE LEGENDS:

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 – 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> day, respectively. C. Average slope of linear regression for individual's nausea rating on each day of experiment. \* -  $p < 0.05$  compared to D1.

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.

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

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, finger 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.

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.

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.







