Sensitisation of Visually Induced Motion Sickness by Prior Provocative Physical Motion

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Abstract

INTRODUCTION Habituation to motion has therapeutic applications for motion sickness desensitisation, and rehabilitation of patients with vestibular disease. Less attention has been devoted to the opposite process: sensitisation.
METHODS Subjects (n=50) were randomly allocated to four sequences: Baseline Visual stimulus; then 15min of time gap; Cross-Coupled motion (C-C) OR a Control condition; then a time gap of 15min OR 2h; Re-test Visual stimulus. Motion exposures were for 10min or until moderate nausea, whichever was sooner. The visual stimulus was a scene rotating in yaw at 0.2Hz with superimposed 'wobble'. C-C was whole-body rotation on a turntable with eight 45° head tilts during each 30s period. Control was head tilt without rotation. Rotational velocity incremented in staircase steps of 3°/s every 30s.
RESULTS Groups were equivalent for Total Motion Sickness Symptom scores elicited by the first visual stimulus (combined: mean+/-SD 10.8+/-8.4). C-C produced greater Total Symptoms (20.3+/-6.8) than Control (3.1+/-3.7). Subjects recovered subjectively from C-C before re-test of visual stimulus. For the re-test visual stimulus, Total Symptoms were higher following C-C (15.1+/-9.0) than following Control (8.3+/-7.1), for both the 15min and 2h re-tests. Sickness Ratings (SR) mirrored these effects of C-C.
DISCUSSION C-C motion sensitised subsequent responses to visual stimulation up to 2h later. Sensitisation of visual stimulation crossed modalities, and appeared subconscious since it occurred despite subjective recovery from C-C. For some individuals, a previously relatively innocuous visual stimulus became nauseogenic on re-test. The results have implications for the use of visual technologies within hours of exposure to provocative motion.

Introduction

Repeated exposure to a stimulus can lead to a reduction in response, a process usually termed habituation. Habituation to motion occurs naturally with repeated exposures to the provocative environment. This process is also incorporated as a core component in motion sickness desensitisation programmes [1, 2] . The process of habituation also has therapeutic applications for rehabilitation of patients with vestibular disease, where graded exercises of head-body movements and repeated exposures to moving visual stimuli are used to reduce symptoms such as dizziness and vertigo [3] . However, less attention has been devoted to sensitisation, which is the opposite process to habituation. In sensitisation, the application again of the same stimulus will cause an increase in response, rather than the decrease which is observed in habituation.

Only three controlled experiments appear to have investigated the process of sensitisation in motion sickness [4, 5, 6] . The question of recovery is of interest in terms of time constants of models of motion sickness onset and recovery [4] . It is also of practical relevance to motion sickness desensitisation programmes employing repeated exposures to provocative motion [1] , since sickness recovery effectively determines the minimum time interval for motion re-challenges [5] . It is noteworthy that sensitisation can still be present after full subjective recovery from a previous stimulus, i.e., in the absence of any conscious experience in terms of current symptoms. A useful concept denoting the subconscious influence of various factors including sensitisation on motion sickness susceptibility is the notion of a “Dynamic Threshold for Nausea “, first coined by Stern [7] .

The model of Oman [4] was based on three successive 10 min challenges (Coriolis stimulation or the wearing of L-R image inverting goggles) with 5 min intervals over a total time period of 45 min. His model contains two parallel pathways of fast (time constant around 1 min, perhaps neuronal) and slow (time constant around 10 min, perhaps neurohumoral) responses, which summate. The study of Golding & Stott [5] used repeated exposures of cross-coupled motion to the point of moderate nausea, at re-test time periods varying from 15 minutes up to 24 hours. Results with re-test intervals up to 60

minutes accorded in general terms with the Oman model. But at two hours re-testing, sensitisation increased, and then at 24 hours later the reverse effect - habituation - was observed. It was hypothesised that the longer-term dynamics of recovery were non-monotonic, as a consequence of some slow oscillation in a neurohumoral system. At even longer time intervals the habituation process becomes revealed. Irmak et al [6] exposed passengers to provocative motion in a car and after subjective recovery then re-tested them with the same motion, this being usually 10 minutes or so later. The results of this study showing sensitisation, were in broad agreement with the model of Oman [4] .

There is an increasing use of visual technologies capable of provoking visually induced motion sickness (VIMS) [8] . Visual technologies are often used in a variety of transport environments capable of provoking motion sickness. It is well known that activities such as using mobile phone screens, monitoring visual displays, etc, may provoke or exacerbate motion sickness if used in a vehicle. However, it is unknown as to whether prior exposure to provocative physical motion might subsequently sensitise a person to VIMS, for example by looking at computer screens or using virtual reality systems after completion of a provocative car ride or boat journey. The aim of this study was to determine whether the response to a visual stimulus which is mildly provocative could be modified (sensitised) by prior exposure motion sickness induced via a different modality, i.e., physical whole-body motion (cross-coupled). The corollary was to confirm that any such sensitisation could occur after subjects were subjectively recovered from prior exposure to cross-coupled motion. A secondary aim was to investigate any relationships between vection (illusory self-motion) and VIMS.

Methods

Subjects.

Subjects were healthy volunteers with normal or corrected normal vision, intact vestibular function and not on any current medication. They were fully briefed, gave informed consent and were free to withdraw at any time. Ethical approval was granted by the Ethics Committee of the University

of Westminster (VRE1617-0007). Subjects (n=50) had mean ages (± SD) 23.9 ± 6.7 years, 42 were women and 8 were men, this sex ratio reflecting the ratio in the university departments from which they were drawn. Subjects' motion susceptibility was assessed using the Motion Sickness Susceptibility Questionnaire MSSQ [9] . Their percentile scores were mean (± SD) 51.4 ± 29.0 %, indicating that the sample were equivalent in susceptibility to the normal population, which has a percentile norm of 50% by definition.

Procedure.

The design used was a randomised design with four parallel arms. The design is shown schematically in Figure 1. Subjects (n=50) were randomly allocated across the four possible sequences: First Visual stimulus; 15 min time gap; then Cross-Coupled (C-C) motion *or* Control (Sham C-C); time gap 15 min *or* 2 h; then Re-test Visual stimulus. The time elapsed since the end of any motion exposure, whether optokinetic or C-C, was of interest in this experiment. However, the exact exposure duration of the motion conditions could not be predicted in advance due to individual differences in susceptibility. Therefore, the elapsed timings (15 min or 2 h) between exposures were zeroed to the end of each motion exposure.

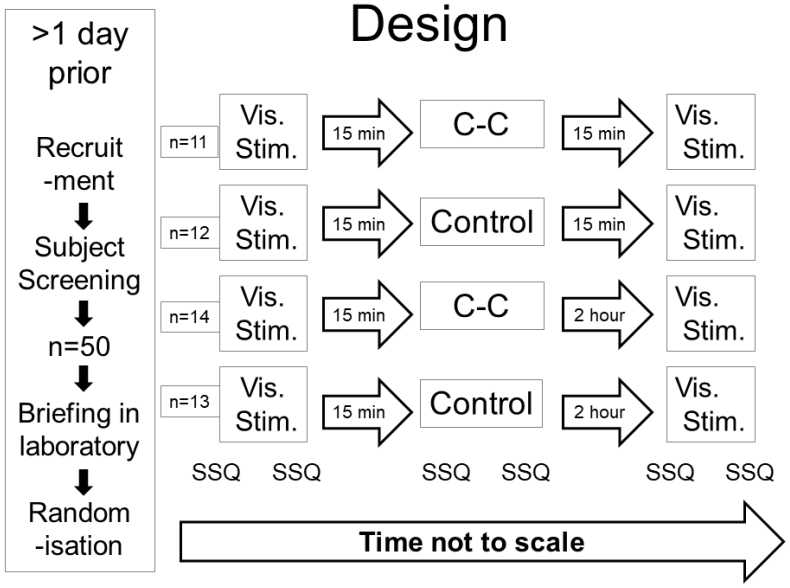

Figure 1: Schematic flowchart of the experimental design where the following abbreviations are used: Vis Stim = Visual Stimulus (optokinetic); C-C = Cross-Coupled (Coriolis) Motion; Control = Sham Cross-Coupled Motion without rotation; SSQ = Simulator Sickness Questionnaire (Total Symptom score). In addition, Sickness Ratings (SR) were measured repeatedly throughout (see Methods for details).

The Visual (Optokinetic) Stimulus was a 360° digital photographic panorama in which the scene was rotated through 360° as if the camera were turning in yaw in a complete circle (Figure 2). The scene used was a 360° panorama as seen from Westminster Bridge over the river Thames, London [10] . The visual scene was projected to be seen as if the subject was rotating at 72°/s about the long axis of their body, tilted from the Earth Vertical by 18° axial tilt. This produced a repetition frequency of the visual features of the 360° scene at 0.2Hz. At the same time an unsteady cyclical movement occurs with an apparent tilting of the horizon reference on the left upwards and simultaneously downwards on the right, a process which then reverses. The repetition cycle of this superimposed visual motion is again at 0.2Hz. This effect we refer to as an apparent 'wobble' of the scene and enhances nauseogenicity [11] . The scene was projected to fill a 2mx2m screen which displayed a 90° segment at any given time. The display had a pixel resolution of 1024x768 at a refresh rate of 60Hz. A comfortable supportive chair was positioned centrally in front of the screen such that, when seated, the distance between the participant's eyes and the screen would be 1.12m. The participant wore a lightweight face mask mounted with a cone through which the subject viewed the screen to restrict the field of view to 83.5° to exclude peripheral vision of the laboratory. The cone gave a circular perimeter to the field of view, which reduced any vertical and horizontal rest frame cues. The reason for the choice of 83.5° was practicality, in terms of the screen dimensions and the need to exclude any reference frame cues of the laboratory. It also maintained methodological consistency with our previous studies. Subjects were instructed to look ahead at the screen and respond to the regular requests to rate their sickness their sickness level on the Sickness Rating scale. Subjects were asked to keep their field of view with the circular mask within the perimeter of the screen but were not asked to look at any specific location or fixation point on the screen. Optokinetic exposures were

for 10 minutes or until moderate nausea (Sickness Rating 4), whichever the sooner. Sickness ratings during visual stimulation were monitored at 1-minute intervals. Recovery after motion was assessed on the sickness rating scale at 1-minute intervals for the first 5 minutes and then at 5-minute intervals thereafter. During the first 5 minutes of recovery period, subjects remained seated to avoid exacerbating symptoms by walking around and stayed seated until recovered.

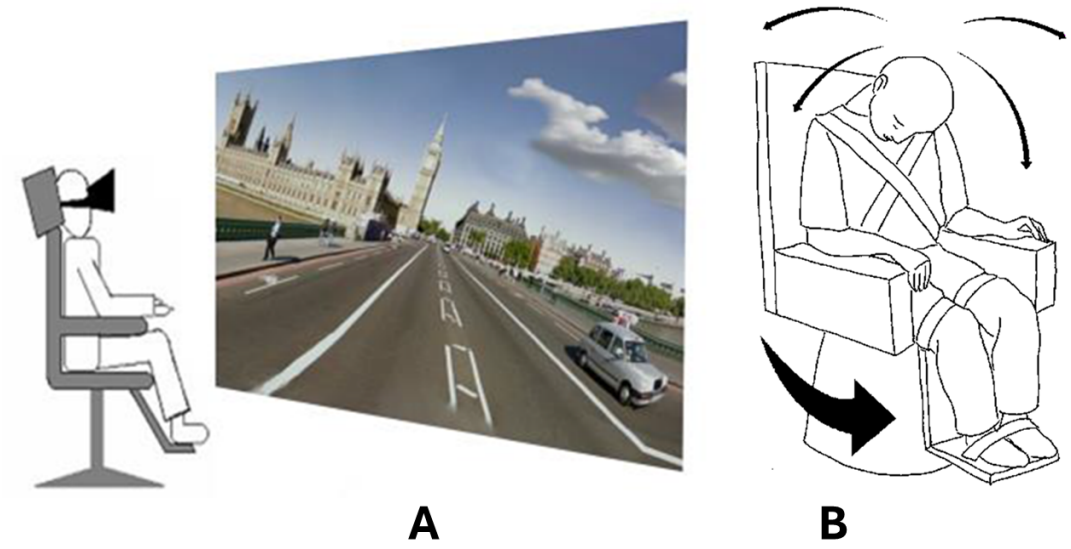

Figure 2: (A) Schematic of the Visual Stimulus: Rotating scene of a complete 360 degrees panorama; Frequency 0.2Hz (72°/s); 'Wobble' 18° axial tilt; Field of View with mask of 83.5° with circular restriction. (B) Schematic of the Cross-Coupled (Coriolis) stimulus (enclosed cabin removed for clarity) showing the head when pitched down. Whole-body rotation on a turntable with eight head tilts of 45° during each 30s period. Rotational velocity incremented as a staircase profile in steps of 3°/s step every 30s.

The Cross-Coupled (Coriolis) Motion Stimulus provoked motion sickness by whole body rotation coupled with head movements which generated cross-coupled (Coriolis) stimulation of the labyrinth (Figure 2). This procedure is extremely nauseogenic and is an established, standardised method of inducing sickness and comparing anti-motion sickness drug treatments [12] . Subjects sat upright with eyes open, with a waist safety restraint, in a chair enclosed in a cabin excluding any view of the external environment. The chair and enclosing cabin assembly was mounted on a

motorised turntable which rotated about an earth vertical axis. Communication was by intercom and subjects were under observation by close circuit television. Subjects were instructed to look move their head to the head rest stops in time with the audio instructions and to respond to the regular requests to rate their sickness their sickness level on the Sickness Rating scale. Subjects were not asked to look at any look at any specific location or fixation point within the illuminated cabin. Commencing from stationary, the rotational velocity was incremented by 3°/s every 30 s following a staircase profile. Guided by pre-recorded audio instructions, subjects made a sequence of 8 head tilts in the four cardinal directions during each 30 s epoch and then rated their sickness level on the sickness rating scale. Tilt excursions were approximately 45° in amplitude to and from padded head rest 'stops'. Motion was stopped at the onset of moderate nausea (Sickness Rating 4) or a maximum time cut-off of 10 min, and then a symptom checklist administered. Recovery after motion was assessed on the sickness rating scale at 1-minute intervals for the first 5 minutes and then at 5-minute intervals thereafter. During the first 5 minutes of recovery period, subjects remained in the stationary apparatus to avoid exacerbating symptoms by walking around. They then transferred to a nearby chair until recovered. In the Control (sham) condition the procedures were exactly the same, except that the chair was not rotated and remained stationary. The sham cross-coupled motion condition lasted for 10 minutes, this being a reasonable estimate of what might be expected for average tolerance to this type of motion based on previous experiments.

The ratings scales and questionnaires used were as follows. Subjects rated sickness on the Sickness Rating scale (SR): 1=no symptoms; 2=initial symptoms of motion sickness but no nausea; 3=mild nausea; 4=moderate nausea; 5=severe nausea and/or retching; 6=vomiting[10]. Initial symptoms but no nausea (SR=2) can include those commonly associated with motion sickness, including stomach awareness, feelings of bodily warmth, sweating, changes in salivation and unusual tastes in the mouth, etc. Sickness was rated on the SR scale every minute during optokinetic stimulation and after each set of eight head movements during cross-coupled motion. The subjects continued to rate sickness ratings during recovery at, 1,2,3,4,5,10

and 15 minutes after stimulation stopped. Recoveries were monitored for ethical reasons and also to ensure recovery before any subsequent stimulus exposure. Immediately before and after optokinetic stimulation or before and after cross-coupled motion, the subject was rated on a symptom checklist (Simulator Sickness Questionnaire, SSQ) [13]. Each symptom was scored: nil=0; mild=1; moderate=2; severe=3; and the scores on the checklist taken at the end of stimulation were summed as a 'Total Symptom Score'. Although three sub-scores (disorientation, oculomotor, and nausea) and a total score can be produced using specific weighting procedures, suggested by the authors of the SSQ, this involves some items being counted twice whereas other are counted only once. Some researchers have failed to find any 3 subscale factor solution but find a 2-factor solution [14]. Consequently, we decided to generate a simple, single overall score by summing the scores for each item for the purposes of simplicity. This has proved a useful approach in our previous experiments [10] and in ship motion surveys in the Southern Ocean [15]. This has the advantage of capturing the greatest amount of data concerning level of motion sickness in a single variable, for subsequent analyses. Individual differences in Motion Sickness Susceptibility were evaluated by a validated questionnaire, the 'MSSQ-short' [9].

Subjects' experiences of self-motion (vection) were also measured after visual stimulus exposure. That is, subjects had to report their level of vection by indicating the percentage of time that they experienced vection during stimulus exposure and its qualitative characteristics (e.g., constant, increasing, decreasing, or varying vection) [10].

Statistical Analysis.

Results were analysed using SPSS V26.0 (IBM Corp, Armonk, NY, USA). Descriptives, t-tests, chi-squared, correlations and ANOVA were employed. For Analysis of Variance (ANOVA) the factor labels used were Group (Cross-coupled versus Control), Retest (15 min versus 2h). Analysis of Covariance (ANCOVA) using the first Visual Stimulus as covariate was employed to analyse the effects of the cross-coupled motion intervention on the second Visual Stimulus. Where statistical tests could be directional, the significances were 2-tailed.

Results

Sickness ratings and symptom scores plotted over time are shown in Figures 3 and 4. As can be seen, sickness ratings and symptom scores increased and then recovered following the first visual stimulus. Symptoms increased markedly with the cross-coupled motion challenge followed by recovery, with the control sham challenge having little effect. Finally, sickness ratings and symptoms score increased in response to the second visual challenge this effect being more marked for subjects who had been previously exposed to cross-coupled motion. These results are analysed in detail in following sections.

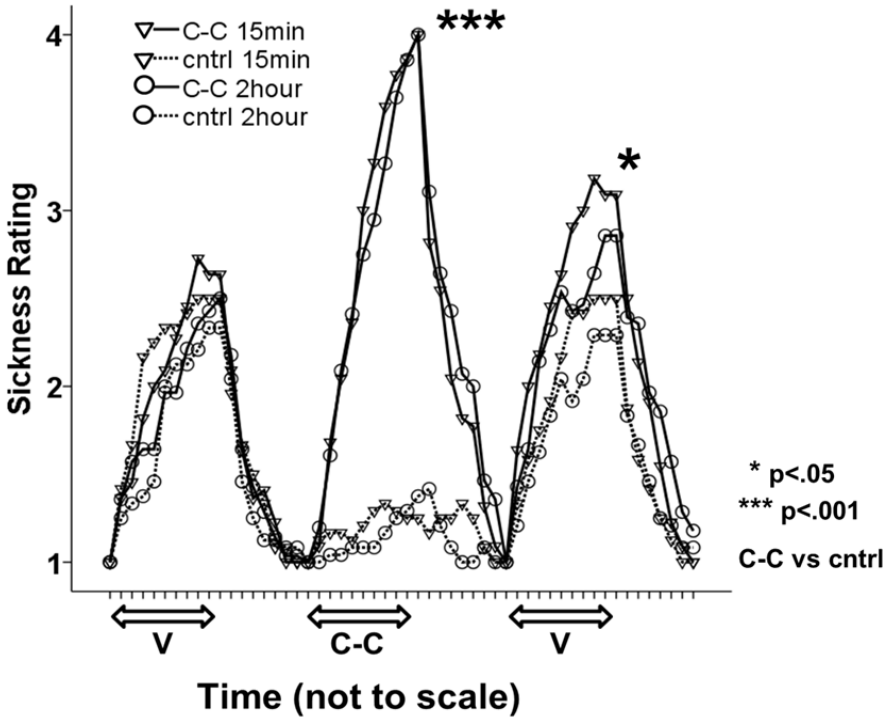

Figure 3: Mean Sickness Ratings (1=O.K.; 2=Initial Symptoms; 3=Mild Nausea; 4=Moderate Nausea) are shown over Time (not to scale) for the four experimental groups. V= Visual Stimulus (optokinetic); C-C= Cross-Coupled (Coriolis) whole body motion; cntrl= Sham Cross-Coupled Motion without rotation. See Figure 1 for design details.

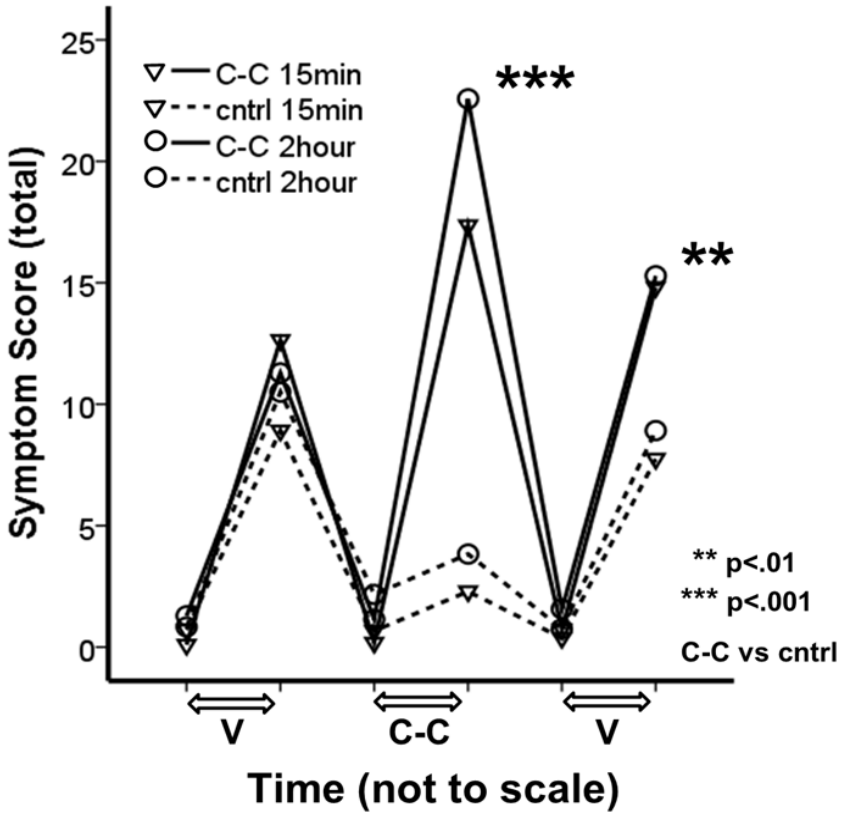

Figure 4: Mean Total Symptom Scores (Simulator Sickness Questionnaire SSQ) are shown over time (not to scale) for the four experimental groups. V= Visual Stimulus (optokinetic); C-C= Cross-Coupled (Coriolis) whole body motion; cntrl= Sham Cross-Coupled Motion without rotation. See Figure 1 for design details.

Since this was a parallel arm design, equivalences between groups at baseline is of importance. These are shown in Table I. As can be seen the four groups were well matched in baseline characteristics including age, sex, intrinsic motion sickness susceptibility (MSSQ) and visually induced motion sickness response to the first visual stimulus. There were no significant differences between groups (See Table I).

Table I. Descriptives and Equivalences Between Groups at Baseline.

Variable	C-C 15 min Vis retest	Control 15 min Vis retest	C-C 2h Vis retest	Control 2h Vis retest	Significance of differences by ANOVA or X^2
Age years	23.5 (3.4)	24.3 (4.4)	21.9 (3.9)	26.0 (11.3)	*p= .454*
Biological Sex, M : F	2 : 9	3 : 9	2 : 12	1 : 12	*p= .691*
MSSQ total	11.9 (10.7)	13.7 (8.9)	12.4 (9.0)	14.9 (9.2)	*p= .853*
MSSQ percentile	47.2 (34.6)	53.0 (28.5)	49.1 (27.8)	55.8 (28.5)	*p= .892*
SSQ after 1st Vis Stim	12.6 (9.5)	8.9 (8.0)	11.3 (9.0)	10.2 (7.3)	*p= .746*
SR after 1st Vis Stim	2.6 (1.4)	2.5 (1.3)	2.5 (1.2)	2.4 (1.0)	*p= .968*

Table notes: Descriptives refer to Mean (SD) or Number. C-C = Cross-Coupled (Coriolis) Motion; Control = Sham Cross-Coupled Motion without rotation; Vis retest = second Visual Stimulus (optokinetic) with retest time following C-C or Control). MSSQ= Motion Sickness Susceptibility Questionnaire; SSQ= Simulator Sickness Questionnaire, Total Symptom score; SR= Sickness Rating where 1=OK through to 4=Moderate Nausea. Numbers are rounded.

Sickness ratings and symptom scores are shown in Figs 3 and 4 and times to sickness rating stages in Table II. Unsurprisingly motion sickness levels in the Cross-coupled condition were very much higher than in the Control (sham) condition. For sickness ratings at motion endpoint, ANOVA revealed that sickness ratings were significantly higher for C-C versus Control as seen in effects for Group ($F=248.5$, df 1,46 $p<.001$), effects were not significant for Retest nor for interaction Group x Retest. ANOVA for numbers of sequences of head movement to achieve Sickness Ratings stages showed that the the C-C condition required far fewer sequences of head movements than Control, i.e. the C-C condition was far more provocative. ANOVA for sequences to achieve Initial Symptoms, showed significant effects for Group ($F=52.1$, df 1,46 $p<.001$) but was not significant for Retest nor for interaction Group x Retest. ANOVA for sequences to achieve Mild Nausea, showed significant effects for Group ($F=131.7$, df 1,46 $p<.001$) but not significant for Retest nor for interaction Group x Retest. ANOVA for sequences to achieve

Moderate Nausea (motion endpoint), showed significant effects for Group (F=44.0, df 1,46 p<.001) but was not significant for Retest nor for interaction Group x Retest. In summary, all these significant findings concerning sequences of head movements to achieve sickness levels showed that C-C was more provocative in producing motion sickness than Control. ANOVA for Total Symptoms at motion endpoint showed highly significant effects for Group (F=118.4, df1,46 p<.001). There was a small effect for Retest (F=6.0, df 1,46 p<.05) but not for interaction Group x Retest. The source of these effects were the much higher Total Symptom scores for C-C versus Control, and slightly higher scores for both C-C and Control for the 2h versus 15min Retest conditions (see Figure 4).

Table II. Mean Sequences of Head Movements to Achieve Each Sickness Rating Level Collapsed Across the Retest Interval Groups.

Intervention Condition	SR level during Cross-Coupled Motion	Mean (SD) Sequences head movements
Cross-Coupled Motion	SR=2 Init. symptoms	4.8 (3.2)
	SR=3 Mild nausea	9.0 (3.8)
	SR=4 Mod. nausea	13.0 (4.4)
Control (Sham C-C)	SR=2 Init. symptoms	15.4 (6.5)
	SR=3 Mild nausea	19.2 (2.3)
	SR=4 Mod. nausea	19.6 (2.0)

Table notes: Descriptives refer Mean (SD) sequences of head movements to achieve each Sickness Rating level for whole-body motion Cross-Coupled (Coriolis) versus Control (sham) intervention, collapsed across the retest interval groups (15 min & 2h). The endpoints are right censored at 20 sequences, equivalent to 10 minutes maximum motion exposure.

As can be seen in Figures 3 and 4, sickness levels for the second Visual Stimulus were higher following the Cross-Coupled motion (C-C) intervention versus Control. ANCOVA was employed to analyse the significance of effects of the C-C intervention on the second Visual Stimulus. For each measure of motion sickness, the equivalent variable from the first Visual Stimulus was employed as the covariate, this procedure helped control for differences in baseline sensitivity. Correlations (r) between the first and second Visual Stimuli are presented with each ANCOVA to provide an estimate of the importance of each covariate.

For severity of sickness at motion endpoint, sickness ratings were significantly higher for C-C versus Control, effect for Group (F=4.2, df 1,45

p<.05, r=.79 p<.001), effects were not significant for Retest nor for interaction Group x Retest. For numbers of sequences of head movement to achieve each Sickness Ratings stage, the C-C condition required less than Control, ie the C-C condition was far more provocative (see Table III). For sequences to achieve Initial Symptoms, there were significant effects for Group (F=5.4, df 1,45 p<.05, r=.60 p<.001) but not significant for Retest nor for interaction Group x Retest. For sequences to achieve Mild Nausea there were significant effects for Group (F=21.3, df 1,45 p<.001, r=.59 p<.001) but not significant for Retest nor for interaction Group x Retest. For sequences to achieve Moderate Nausea (motion endpoint), there was a marginally significant effect for Group (F=3.9, df 1,45 p=.056, r=.74 p<.001) but not significant for Retest nor for interaction Group x Retest. Total Symptoms at motion endpoint showed highly significant effects for Group (F=7.9, df1,45 p<.01, r=.66 p<.01) but not significant for Retest nor for interaction Group x Retest.

In summary, all these measures for the second Visual Stimulus showed higher levels of motion sickness following the C-C intervention versus Control. Importantly, all differences between the effects of the 15min versus 2h retest were not significant, suggesting broad equivalence between the strength of subsequent effects of C-C versus Control, despite the differing re-test time intervals.

Table III. Summary Mean Times to Achieve Each Sickness Rating Level Collapsed Across the Retest Interval Groups.

Intervention Condition	SR level during Visual Stimulus	Pre (1st) Visual Stimulus	Post (2nd) Visual Stimulus
Cross-Coupled Motion	SR=2 Init. symptoms	4.8 (3.6) mins.	3.3 (3.4) mins.
	SR=3 Mild nausea	7.6 (3.0) mins.	5.6 (3.2) mins.
	SR=4 Mod. nausea	8.7 (2.1) mins.	7.7 (2.6) mins.
Control (Sham C-C)	SR=2 Init. symptoms	4.9 (3.7) mins.	5.2 (3.6) mins.
	SR=3 Mild nausea	6.9 (3.4) mins.	8.1 (2.9) mins.
	SR=4 Mod. nausea	8.8 (2.3) mins.	8.7 (2.3) mins.

Table notes: Descriptives refer to Mean (SD) times in minutes to achieve each Sickness Rating level for Visual stimulus (1st) pre- and Visual Stimulus (2nd) post- cross-coupled or control interventions, collapsed across the retest interval groups (15 min & 2h). The endpoints are right censored at 10 minutes maximum visual stimulus exposure time.

It was observed that some subjects found the first visual stimulus to be relatively innocuous and did not experience nausea. But for these individuals, the visual stimulus became nauseous on re-test. The following analysis was on this limited subset of individuals, i.e., only those who went from experiencing no nausea in the first visual stimulus, then becoming nauseous in second visual stimulus after C-C. Given this, it was necessary to amalgamate observations to provide the necessary numbers for statistical testing. Data were collapsed across re-test intervals and sickness levels were divided into absence of nausea versus nausea. For the C-C group (n=25), 14 subjects experienced no nausea for first visual stimulus, and 6 of these subjects went on to experience nausea on re-test after C-C. For the Control group (n=25) this change was much rarer, 13 subjects experienced no nausea for first visual stimulus, and only 2 of these subjects went on to experience nausea on visual re-test after Control C-C. This difference between C-C (6/14) vs Control (2/13) was significant (Binomial test for observed proportion in C-C vs expected proportion from Control, $p<.001$).

There were no significant effects for changes in percentage of time that vection was experienced between the first and second visual stimulus, nor for Group, Retest or Group x Retest, nor for qualitative aspects of vection: constant, increasing, decreasing, or varying. For brevity these are not reported in detail. The test-rest reliability of vection between first and second visual stimulus was $r=.52$ ($p<.001$). Of interest were possible individual differences relationships between vection and VIMS. Correlations between vection as percentage of time that vection was experienced and severity of VIMS were as follows, first visual stimulus $r=.31$ ($p<.05$) with Sickness Rating, $r=.40$ ($p<.001$) with Total Symptom Score, and for the second visual stimulus $r=.27$ (p=ns) with Sickness Rating, $r=.35$ ($p<.05$) with Total Symptom Score. Re-analysing the data by C-C versus Control groups did not improve these correlations but simply reduced statistical significances.

Discussion

The aim of this experiment was to investigate the effects of exposure to provocative whole-body cross-coupled motion on subsequent exposure to

visual motion. The results showed that prior exposure to cross-coupled motion sensitised the visually induced motion sickness (VIMS) response to subsequent visual stimulation. This sensitisation lasted for up to two hours. Moreover, sensitisation appeared to be subconscious since it occurred despite subjective recovery from the preceding cross-coupled motion. Notably for some individuals, what had been a formerly relatively innocuous visual stimulus without experience of nausea, then became nauseous on re-test after cross-coupled motion.

The findings of this study, i.e. objectively observed sensitisation despite subjective recovery, are in broad agreement with previous findings for re-test time periods around a quarter of an hour or so [4, 5, 6] and are consistent with the only study which extended re-tests observations up to two hours later [5] . In those experiments the same type of physical motion or visual stimulus was repeated, whereas here we have shown for the first time that this sensitisation can cross different modalities of motion, physical to visual. How long such sensitisation might persist beyond two hours is unknown. Presumably it would weaken over time. Certainly, by 24 hours later, it would be expected to change into the opposing process of habituation based on observations using repeated cross-coupled motion [5] . Interestingly this hypothesis can be examined. In the control condition, comparison of the first versus second visual stimuli indicates a small (non-significant) decrease in VIMS response to the second visual stimulus (see Figure 4). This may suggest that for a relatively weaker provocative visual stimulus, the process of habituation may overtake that of sensitisation sooner than might be expected for a highly provocative stimuli such as repeated cross-coupled motion [5] .

Several possible mechanisms can be proposed to explain the present observations on sensitisation. The most plausible is that the Nucleus Tractus Solitarius of the brainstem together with associated brainstem nuclei of the medullary reticular formation, form a network which acts as a central integrator for incoming emetic signals [16] . Such emetic inputs to this central integrator include those from the vestibular system, vagal afferents from the gut, blood toxin detectors in the Area Postrema, and even descending cortically processed emotional signals such as extreme fear. In the present study, the emetic signals from cross-coupled motion would be retained below

conscious perception for an amount of time in the integrator and then summated with those from the second visual stimulus leading to the observed sensitisation. An alternative explanation may be couched in terms of classical conditioning of nausea. This is analogous to that observed with cancer chemotherapy patients feeling sick just at the sight the chemotherapy treatment centre (conditioned stimulus) when returning for repeated courses of highly emetic chemotherapy (unconditioned stimulus) [17] . Similar examples are the passenger who becomes sick as soon as he or she steps aboard the aircraft or the student pilot who develops symptoms after a short time in the air, irrespective of the intensity of the motion stimuli experienced [1] . However, a classical conditioning mechanism seems unlikely in this experiment, since the conditioned stimulus would not be the same. Both the rooms and the stimulus apparatus for cross-coupled and visual motion were very different, i.e., different putative conditioned stimuli. Moreover, such classical conditioning should cause anticipatory conditioned nausea at the start of the second visual stimulus, but subjects did not report such an effect (see Figures 3 & 4).

Finally, in terms of the sensory conflict or mismatch theory of motion sickness, it could be hypothesised that the cross-coupled intervention reset the expected relationships between vestibular, visual and proprioceptive sensory inputs, of the internal model [1] . Such “re-setting” might be seen also as analogous to the processes involved in mal-de-debarquement [18] or perhaps the ‘flashbacks’ that some pilots may experience several hours after simulator training [19] . Although not disprovable, such effects usually require longer exposure in altered motion environments, for mal-de-debarquement days in sea voyages or in micro-gravity in space, or for ‘flashbacks’ an hour or more of simulator training. In contrast, here, the sensitising exposure was 10 minutes or less.

There were no significant effects for changes in percentage of time that vection was experienced between the first and second visual stimulus, nor for effects of cross-coupled motion, re-test time period, interactions, nor for any qualitative aspects of vection. The relationship between the amount of time vection was experienced and VIMS was generally weak, varying between non significance to significance. In previous studies using this type of visual

stimulus no significant relationships were found between vection and VIMS [10, 11, 20] . However, the reason that this study did find significant relationships may simply have been that the larger sample size allowed detection of low correlations at statistical significance. Although some studies have found relationships between vection and VIMS [21] , the literature is contradictory with frequent failures to show such relationships [22, 23, 24] . A notable feature of vection is that this illusion can onset and then vanish within seconds, whereas motion sickness usually builds up more slowly over time. Vection may play a role in VIMS but the relationship between them is not one-to-one and does not appear be directly causal in any obvious fashion. The explanation may be that vection is a conscious illusory perception, presumably happening at a cortical level in the brain. In contrast, the visual vestibular mismatches or conflicts provoking motion sickness are doubtless occurring at the brainstem–cerebellar level [25] and may not be directly accessible to conscious perception. Across studies, this may explain the lack of a consistent association between vection and VIMS.

This study had a number of limitations. Sensitisation of VIMS was tested up to two hours following the cross-coupled intervention. Although we might expect it to diminish over time, how long such sensitisation might persist beyond two hours is unknown and deserves investigation. Moreover, it could be one contributory cause of ‘functional’ disorders [3] in which a sufferer experiences malaise and disorientation in apparently innocuous circumstances. The provocative VIMS stimulus was continuous wide field visual motion and the intervention employed in this experiment was cross-coupled motion. The generalisability of these effects remains to be investigated with respect to both VIMS elicited by other visual stimuli, including virtual reality systems, also to sensitisation provoked by other types of physical motion such as that of ships, land vehicles, or aircraft. Equally the reverse of this, i.e., any effect of VIMS on subsequent provocative physical motion was not explored. However, since it is probable that the severity of the motion stimulus is responsible for the sensitisation effects, it is more likely that C-C motion will sensitise VIMS from visual stimulation than vice-versa, because C-C motion is more provocative than visual. There were some indications of low levels of symptoms during the C-C control condition. It is

unlikely that insufficient recovery is the explanation since subjects were fully recovered before the start of C-C on the SR scale (Fig 3) and for the SSQ total symptoms the scores were not significantly different from the baseline before the first visual stimulus. The control C-C involved performing repeated head movements but in absence of rotation, so it is possible that repeated head movements by themselves may have produced low level symptoms. This might have caused a slight underestimate of the magnitude of the C-C sensitisation effect *versus* control C-C on the second visual stimulus. This could be addressed by an additional static control C-C condition without head movements but would greatly increase the complexity of the experiment. However, these observations did not alter the main conclusion of the study. A field of view of 83.5° was employed, and it is possible that a wider field of view might increase the relationship between magnitude of vection and VIMS. Finally, although the subjects had intrinsic motion sickness susceptibility equal to the general population as measured by the MSSQ, men and older people were under-represented.

In conclusion, prior exposure to cross-coupled motion sensitised subsequent responses to visual stimulation up to two hours later. This sensitisation of visual stimulation crossed modalities (ie, physical motion to visual motion) and appeared subconscious since it occurred despite subjective recovery from the prior cross-coupled motion. Indeed, for some individuals, what had been a formerly relatively innocuous visual stimulus became nauseogenic on re-test. This has implications for use of visual technologies hours after exposure to provocative motion.

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