Transportation Research Part F 47 (2017) 42–58

Contents lists available at ScienceDirect

Transportation Research Part F

journal homepage: www.elsevier.com/locate/trf

The use of transdermal scopolamine to solve methodological issues raised by gender differences in susceptibility to simulator sickness

Romain Chaumillon [a,*], Thomas Romeas [a], Charles Paillard [a], Delphine Bernardin [a,b], Guillaume Giraudet [a,b], Jean-François Bouchard [c], Jocelyn Faubert [a]

[a] Visual Psychophysics and Perception Laboratory, School of Optometry, Université de Montréal, 3744 Jean-Brillant, Montréal, Quebec H3T 1P1, Canada
[b] Essilor Canada Ltd., Montréal, Quebec, Canada
[c] Neuropharmacology Laboratory, School of Optometry, Université de Montréal, 3744 Jean-Brillant, Montreal, Quebec H3T 1P1, Canada

ARTICLE INFO

Article history:
Received 13 October 2016
Received in revised form 2 March 2017
Accepted 11 April 2017

Keywords:
Cybersickness
Anticholinergic drug
Motion-based driving simulator
Sex difference
Methodology

ABSTRACT

While car driving simulators are an essential research tool for assessing drivers' behavior under safe and controlled conditions, gender differences in susceptibility to simulator sickness is a major drawback for the interpretation of the outcomes. The present study assessed the efficacy of a technological (**Experiment 1**; the use of motion-based driving simulator) and a pharmacological (**Experiment 2**; the use of transdermal scopolamine) solution to solve the methodological issues raised by gender differences in susceptibility to simulator sickness. In experiment 1, twenty-four women and twenty-four men performed two driving sessions lasting 16 min within a high-fidelity motion-based driving simulator. In experiment 2, eight women and eight men were tested in the same simulator but received, in a counterbalanced between subjects design, either a placebo or a scopolamine patch 12 h before the experimentation. In both experiments, simulator sickness questionnaire scores were computed before the first driving session and after the first and the second driving sessions. The results showed that only the pharmacological solution was efficient for solving these methodological issues. Indeed, whereas women experienced greater simulator sickness than men under placebo influence ($p < 0.01$) there was no gender difference in susceptibility to simulator sickness following the transdermal scopolamine administration ($p > 0.05$). As a whole, this demonstration paves the way toward better-controlled experiments. Moreover, beyond their implications in many research fields, the results from car driving simulator studies are of use to road safety policy makers. Thus, this approach allowing cancellation of gender differences in susceptibility to simulator sickness is of critical importance at a society level.

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* Corresponding author.
E-mail addresses: romain.chaumillon@umontreal.ca (R. Chaumillon), thomas.romeas@umontreal.ca (T. Romeas), charles.paill@hotmail.fr (C. Paillard), dtranvouez-bernardin@essilor.ca (D. Bernardin), giraudeg@essilor.fr (G. Giraudet), jean-Francois.bouchard@umontreal.ca (J.-F. Bouchard), jocelyn.faubert@umontreal.ca (J. Faubert).

http://dx.doi.org/10.1016/j.trf.2017.04.003
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1. Introduction

Virtual reality is a promising technology which has progressed considerably in recent years with the development of many scientific, industrial, military, and clinical applications. One of the biggest advantages of virtual reality is that it allows the accurate study of behaviors in a safe, cost-effective and experimentally controlled environment. Considering that driving is the principal mode of travel for adults in many countries (Hu & Reuscher, 2004), car driving simulators have become essential tools to ensure public safety. As such, car driving simulators have shown their efficiency in training young unexperienced drivers and for judging driving abilities in many populations (i.e. Allen, Park, Cook, & Fiorentino, 2012; Casutt, Theill, Martin, Keller, & Jäncke, 2014; de Winter et al., 2009; Pollatsek, Vlakveld, Kappe, Pradhan, & Fisher, 2011; Unsworth & Baker, 2014). Nevertheless, this technology is strongly limited in its experimental use due to the steady occurrence of a general feeling of being unwell which appears after approximately 10 min within the driving simulator (Lin et al., 2007; Park et al., 2008). Such a major drawback, known as simulator sickness phenomenon (Kennedy & Fowlkes, 1992; McCauley & Sharkey, 1992), is a unique form of motion sickness (Rizzo, Sheffield, Stierman, & Dawson, 2003) and entails different symptoms varying from a mere feeling of unpleasantness to strong nausea and vomiting (Blade & Padgett, 2002; Chance, Gaunet, Beall, & Loomis, 1998).

Beyond its unpleasant symptoms, simulator sickness can potentially confound data and limit the effectiveness of experimentation (Helland et al., 2016; Lerman et al., 1993). Even more worrying for experimental measures quality, studies performed in virtual environments as a whole revealed large individual differences in susceptibility to motion sickness as a function of numerous factors, including age (Brooks et al., 2010; Bélanger, Gagnon, & Yamin, 2010; Mullen, Weaver, Riendeau, Morrison, & Bédard, 2010; Roenker, Cissell, Ball, Wadley, & Edwards, 2003; Shanmugaratnam, Kass, & Arruda, 2010), number of past exposures to virtual environments (Domeyer, Cassavaugh, & Backs, 2013; Kennedy, Stanney, & Dunlap, 2000), postural instability (Smart, Stoffregen, & Bardy, 2002), and gender (Classen, Bewernitz, & Shechtman, 2011; Flanagan, May, & Dobie, 2005). In particular, the higher susceptibility to motion sickness in women than in men is one of the most commonly observed phenomenon.

Car driving simulator studies demonstrated that gender differences were not restricted to motion sickness but also extended to simulator sickness in the way that women suffer greater simulator sickness symptoms than men (Matas, Nettelbeck, & Burns, 2015; Mourant & Thattacherry, 2000; Park, Allen, Fiorentino, Rosenthal, & Cook, 2006; Park et al., 2008; Yoo, 1999). As an important consideration, all the aforementioned studies were performed on fixed-base simulators. Because simulator sickness also depends on environmental characteristics such as how realistic a device is (e.g. Domeyer et al., 2013), gender differences in high-fidelity motion-based driving simulator might be different than those observed in lower-fidelity fixed-base driving simulators. Moreover, the most widely accepted theory claims that the simulator sickness might result from a conflict between sensory information (Reason & Brand, 1975). Then, the greater correspondence between visual, somatosensory and vestibular motion cues stemming from motion-based driving simulators might reduce simulator sickness. Nevertheless, the few studies addressing this question of differences between fixed-base and motion-based simulators found totally opposite results: whereas Curry, Artz, Cathey, Grant, and Greenberg (2002) evidenced greater simulator sickness in fixed-base than in motion-based simulator, Dziuda, Biernacki, Baran, and Truszczyński (2014) showed higher simulator sickness in motion than in fixed-base platform. More importantly for our purpose, to the best of the authors' knowledge, only one study, led by Garcia et al., in 2010, addressed the question of gender differences in this context. The authors recorded the simulator sickness questionnaire (SSQ; Kennedy, Lane, Berbaum, & Lilienthal, 1993) scores of 8 women and 8 men, while they were engaged in a driving task within either a rotating-base or a fixed-base simulator. A slight downward trend was observed in women when the driving task was performed in the rotating-base simulator compared to the fixed-base simulator. Nevertheless, the greater correspondence between visual, somatosensory and vestibular motion cues allowed by motion-based simulator failed to clearly show efficiency in reducing simulator sickness.

The genesis of simulator sickness is not fully understood but researchers attempting to explain this phenomenon have proposed several hypotheses. According to the three most widely accepted theories, simulator sickness might be caused by either: (i) a conflict between the actual visual, vestibular and somatosensory inputs and the expected internal model that one builds from daily life experience (Reason & Brand, 1975). (ii) Postural instability produced by anticipation of the forces that would be experienced with the motion (Riccio & Stoffregen, 1991). (iii) Repeated eye movements that create traction of the extraocular muscles stimulating the vagus nerve (Ebenholtz, 1992). Whatever case that one considers, there are still no accepted explanations for why women are more susceptible to simulator sickness than men. Until a complete and universal explanation is able to determine the precise origin of motion or/and simulator sickness as well as predict its intensity depending on individual characteristics, it remains fastidious to eliminate symptoms.

Despite the lack of a profound theory, several countermeasures against simulator sickness have been proposed. Most of them include an adaptation of the experimental setup and/or procedure in order to minimize the likelihood of feeling sick. For instance, it has been advised to use an adaptation period with repeated expositions (Domeyer et al., 2013; Teasdale, Lavalliere, Tremblay, Laurendeau, & Simoneau, 2009), use shorter scenarios (Cassavaugh, Domeyer, & Backs, 2011), limit turns, pitch and roll movements (Balk, Bertola, & Inman, 2013; Mourant, Rengarajan, Cox, Lin, & Jaeger, 2007; Stoner, Fisher, & Mollenhauer, 2011) reduce the field of view available (Johnson, 2005) or decrease the driving speed (Mourant & Thattacherry, 2000). Importantly, all these restrictions raise the non-negligible problem of dwindling experimental possibilities though these possibilities are one of the driving simulator's main advantages. Conversely, pharmaceutical treatment is

also an efficient preventative option to treat motion sickness (see Golding & Gresty, 2015; Shupak & Gordon, 2006) and does not require adapting experimental conditions.

In 1970, Wood & Graybiel established that motion sickness is linked to a cholinergic stimulation and is stamped out by adrenergic activation. Following this statement, the anticholinergic drugs have been widely used to prevent motion sickness (Hoyt, Lawson, McGee, Strompolis, & McClellan, 2009). While several different anticholinergic drugs have been tested, scopolamine appeared to be the most effective anti-motion sickness drug (Golding & Gresty, 2015; Nachum, Shupak, & Gordon, 2006; Shupak & Gordon, 2006; Spinks & Wasiak, 2011). The mechanism of action of scopolamine, albeit not totally known, is believed to inhibit both the integration of sensory stimuli (by blocking cholinergic transmission from vestibular nuclei to higher central nervous system centers) and cholinergic fibers linking the vestibular apparatus to the vomiting center (Antor et al., 2014; de Waele, Mühlethaler, & Vidal, 1995; Renner, Oertel, & Kirch, 2005). When considering the "sensory conflict and neural mismatch theory" (Reason & Brand, 1975), such inhibition would allow a reduction in the discrepancies between sensed and expected vestibular information, thus resulting in decreased simulator sickness. Despite a huge literature about the effectiveness of scopolamine on motion sickness (see Brainard & Gresham, 2014; Golding & Gresty, 2015; Zhang et al., 2016 for recent reviews), we are not aware of any attempt to investigate its influence on simulator sickness related to motion-based driving simulators nor on potential gender differences in scopolamine effectiveness.

Thus, the purpose of the present experimentation was two-fold. Since only a single, inconclusive study has investigated potential gender differences in motion-based simulators (Garcia et al., 2010), the first part of our study (**Experiment 1**) has been designed as a preliminary experiment with the aim of determining whether gender differences in susceptibility to simulator sickness are still present within a high-fidelity motion-based driving simulator. In a second part (**Experiment 2**), we tested whether transdermal scopolamine might be an effective tool to reduce simulator sickness and cancel gender differences in motion-based driving simulators.

It was predicted that (**1**) simulator sickness and consequently, gender differences, would be less significant within our motion-based simulator compared to previous studies using a fixed-based simulator and that (**2**) transdermal scopolamine administration would allow the minimization of simulator sickness and gender differences in susceptibility to simulator sickness to a greater extent.

2. Experiment 1: Gender differences in motion-based driving simulator

2.1. Material and methods

2.1.1. Participants

Forty-nine participants (mean age ± SD = 25.2 ± 2.6 ranged from 22 to 31.4 years old) were recruited after having provided a signed written consent for their inclusion. All participants were healthy, reported normal or corrected-to-normal vision and showed no sign of neurological disorders. A preliminary examination allowed us to ensure that each participant met our criteria for inclusion (i.e. possessing a valid driver's license, good level of mobility for arms and legs movements, visual acuity equal or superior to 6/6 on the Snellen test and an absence of medication at least 48 h before the experimentation). The study adhered to the tenets of the Declaration of Helsinki (last modified, 2004) and the procedure was approved by the ethics committee of Université de Montréal. In order to test our hypothesis, participants were classified based on their gender, giving rise to two experimental groups: 25 women (mean age ± SD = 25.6 ± 3.7 years old) and 24 men (mean age ± SD = 24.9 ± 1.9 years old). Note that one woman dropped out of the experiment due to unbearable simulator sickness. This dropout rate of 2.04% is in line with previous studies involving young people in driving simulators (Bélanger et al., 2010; Kaber, Zhang, Jin, Mosaly, & Garner, 2012; Kawano et al., 2012).

2.1.2. Simulator sickness questionnaire

We used the Simulator Sickness Questionnaire (SSQ; Kennedy et al., 1993) as it is a reliable tool for assessing symptomatic responses to our motion-based driving simulator. The SSQ is a modification of the Motion Sickness Questionnaire (MSQ; Kellogg, Kennedy, & Graybiel, 1965) customized to suit the purposes of characterizing motion sickness experienced in virtual environments. The SSQ involves 16 items, each concerning a specific symptom which may be experienced in a virtual reality context. For each item, the participant indicates how much the symptom is affecting his behavior by referring to a 4-point scale of intensity (0 = no symptom; 1 = slight; 2 = moderate; 3 = severe). The factor analytic model used in Kennedy et al. (1993) evidenced that these symptoms may be grouped in three orthogonal classes of symptoms: Oculomotor discomfort (O; *e.g.* eyestrains, blurred vision and headaches), Disorientation (D; *e.g.* vertigo and dizziness) and Nausea (N; *e.g.* vomiting and salivation increased) symptoms. We followed Kennedy et al.'s scoring procedure for each class of symptom and for the overall simulator sickness measure (*i.e.* total score). Thus, each symptom variable score was multiplied by an appropriate weight and the weighted values were summed to obtain the weighted total. The O, D and N scores were then calculated from the weighted totals using the conversion formulas (these formulas are visible in Table 4 of Kennedy et al. (1993)). The total score was obtained by summing all the weighted totals (i.e. O + D + N) and applying the total score conversion formula. The SSQ questionnaires were administered either in English or in French for non-bilingual participants (see Bouchard, Robillard, & Renaud, 2007; Bouchard, Robillard, Renaud, & Bernier, 2011; Bouchard, St-Jacques, Renaud, & Wiederhold, 2009 for more information about the French-Canadian validated version).

2.1.3. Experimental setup

The driving sessions were performed in a VS500M car driving simulator (Virage Simulation Inc.®). Participants were sitting in a high-fidelity, motion-based, driving simulator which faithfully reproduced the controls and indicators that are found on the steering wheel as well as the dashboard and pedals of an interior vehicle (see Fig. 1). The vehicle was controlled by moving a force-loaded steering wheel in a typical driving manner and depressing the accelerator and brake pedals accordingly.

The computerized driving simulation task was displayed under ambient lighting on three plasma screens (screen size: 50 in.; screen resolution: 1280 × 720 pixels), providing a 180° field of view. Additionally, there were rear and side mirrors and two additional screens placed behind the participant allowing to check the blind spots. The immersive experience was also enhanced by motion and auditory cues. The motion system consists of a compact three-axis platform with electric actuators and provided acceleration cues, engine vibration and road texture feedback as a function of the car speed (frequency up to 100 Hz). An on-board stereo sound system correlated with the speed and road texture provided naturalistic engine sounds and external road noise. To be more realistic, the acoustic system also simulates a Doppler effect to display the sounds of passing traffic.

2.1.4. Task and protocols

The experimental session began with the pre-exposure SSQ (*i.e.* SSQ0) which will be subsequently used as an individual reference for the data exploration of post-exposure questionnaires (*i.e.* SSQ1 and SSQ2; Regan & Price, 1994). After the completion of this SSQ0, participants were engaged in the first driving session. The task demanded that participants behave and navigate in an efficient adaptive manner through a downtown urban environment with a moderate traffic density. They were instructed to drive as they normally would and follow visual and oral orientation instructions while respecting road signage, other road users as well as speed limitations. The average length of one scenario was 4 min and included 6 left turns, 3 right turns, 2 stops and 8 traffic lights. This scenario, with its multiple turns and transient stops, was chosen to facilitate the simulator sickness onset. The same scenario was repeated 4 times (*i.e.* a session lasted approximately 16 min). In order to limit the adaptation phenomenon, the itinerary was similar but the conditions such as pedestrians and cars changed. Immediately after the first driving session, participants were asked to complete the first post-exposure questionnaire (*i.e.* SSQ1) and rested during the following 30 min. After this break, participants were engaged in the second driving session which was identical in all respects to the first one. Finally, they completed the second post-exposure questionnaire (*i.e.* SSQ2).

2.1.5. Statistical analysis

The SSQ scores were registered at three different times: before the first driving session (SSQ0), after the first driving session (SSQ1) and after the second driving session (SSQ2). To evaluate the potential influence of gender on simulator sickness intensity, the total scores registered in the three SSQ sessions were submitted to a between (Gender: Women, Men) by within (SSQ_session: SSQ0, SSQ1, SSQ2) bootstrapped ANOVA (**see details below**) with repeated measures on the last factor. In a subsequent analysis, we aimed to accurately study the effect of gender on the three classes of symptoms considered in the SSQ score computation (*i.e.* Oculomotor discomfort, Disorientation and Nausea; see **part 2.1.2.**) obtained in the three different sessions (i.e. SSQ0, SSQ1 and SSQ2). The use of separate analyses for each session stressed the need to correct the SSQ values obtained in SSQ1 and SSQ2 with the "basal threshold" (*i.e.* SSQ0) from each subject (see Regan & Price, 1994). Therefore, for each subject and each symptom, SSQ0 scores were subtracted from those registered in SSQ1 or in SSQ2 sessions leading to obtain new weighted scores of Oculomotor discomfort (Ow), Disorientation (Dw) and Nausea (Nw) for SSQ1 and SSQ2 sessions. The weighted scores were each submitted to a between (Group: Women, Men) by within (Symptoms: Ow, Dw, Nw) bootstrapped ANOVA for each of the three sessions.

Fig. 1. The VS500M car driving simulator (Virage Simulation Inc.®) used in the present study.

The distributions of the SSQ scores did not meet the essential assumptions of sphericity and homoscedasticity, preventing the use of parametric ANOVAs. To deal with this issue, we used a non-parametric bootstrap-based ANOVA method (number of iterations = 1000; percentile bootstrap) which allows to maintain the Type I error rate of our tests at its nominal level and to maintain the power of the tests, even when the data are heteroscedastic and do not show normal distributions (Wilcox, 2011; Wilcox, 2012; see also Erceg-Hurn & Mirosevich, 2008). When performing multiple comparisons, we used the Hochberg's method to control the Familywise error rate (Hochberg, 1988; Wilcox, 2011; Wilcox, 2012). This method allows to adapt the acceptance threshold of the alpha value (hereinafter called critical alpha value; $\alpha crit$).

To provide information about the magnitude of effects, the effect sizes are reported. The computation of effect sizes is subject to the same assumptions of sphericity and normality as the ANOVA. For this reason, we estimated effect sizes using the robust Cohen's d (d_r; Algina, Keselman, & Penfield, 2005a; Algina, Keselman, & Penfield, 2005b; Algina, Keselman, & Penfield, 2006; *see also* Erceg-Hurn & Mirosevich, 2008) rather than with the classic Cohen's d. The computation of the d_r will also be based on bootstrap method. To be consistent with non-parametric bootstrapped ANOVA, we fixed the number of iterations to 1000. Rules concerning the interpretation of d_r are the same as those concerning classical Cohen's d values. Accordingly, the effect sizes (*i.e.*, d_r) close to .20, .50 or .80 will be considered as small, medium and large, respectively (Cohen, 1988).

2.2. Results

2.2.1. Gender and simulator sickness susceptibility

Means of the SSQ scores obtained in the 24 women and 24 men in the three different sessions (*i.e.* SSQ0, SSQ1 and SSQ2) are shown in Fig. 2. The statistical analysis revealed a significant effect of Gender [$F(1,46) = 9.37$; $p = .002$; $d_r = .96$], a significant effect of SSQ_session [$F(1,46) = 38.11$; $p < .001$] and a significant interaction between Gender and SSQ_session factors [$F(1,46) = 9.04$; $p = .002$]. This pattern of results demonstrates that women were more susceptible to simulator sickness than men. The multiple pairwise comparisons performed on the SSQ_session factor demonstrated that, regardless of the gender, SSQ0 scores were significantly smaller than SSQ1 ($p < .001$; $\alpha crit = .025$; $d_r = .88$) and SSQ2 scores ($p < .001$; $\alpha crit = .017$; $d_r = .94$) whereas SSQ1 and SSQ2 scores were not statistically different ($p = .17$; $\alpha crit = .05$; $d_r = .1$). Interestingly, the breakdown of the significant interaction between Gender and SSQ_session factors revealed no gender difference before the first driving session (*i.e.* SSQ0; $p = .67$; $\alpha crit = .05$; $d_r = .19$), a strong tendency to more simulator sickness in women (M = 52.2; SEM = ± 8.23) than in men (M = 23.38; SEM = ± 5.29) after the first driving session (*i.e.* SSQ1; $p = .057$; $\alpha crit = .017$; $d_r = .78$) and a significantly greater amount of simulator sickness in women (M = 61.08; SEM = ±8.51) than in men (M = 25.71; SEM = ±7.93) after the second driving session (i.e. SSQ2; $p < .001$; $\alpha crit = .006$; $d_r = 1.02$). Additionally, the evolution of simulator sickness through the two SSQ sessions which followed a driving session (*i.e.* SSQ1 and SSQ2) seemed to be different between women and men. Indeed, whereas women strongly tended to experience more simulator sickness during the second driving session than during the first driving session ($p = .046$; $\alpha crit = .013$; $d_r = .14$), men showed no difference between the two driving sessions ($p = .62$; $\alpha crit = .025$; $d_r = .02$). This pattern of results means that the higher the exposure, the greater the difference between women and men widens.

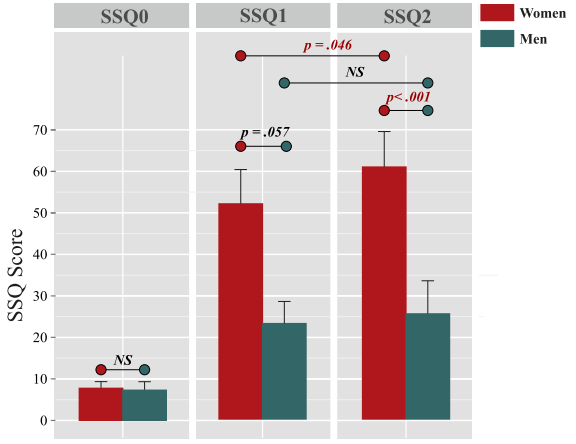

Fig. 2. Means of the total SSQ scores obtained in women (red bars) and men (green bars) groups through the three different sessions. The analysis revealed a significant effect of Gender, a significant effect of SSQ_session and a significant interaction between Gender and SSQ_session factors. The multiple pairwise comparisons showed that there was no gender difference before the first driving session (*i.e.* SSQ0, left panel). After the first driving session (*i.e.* SSQ1; middle panel), women strongly tended to show more simulator sickness than men. After the second driving session (*i.e.* SSQ2, right panel), women were significantly more susceptible to simulator sickness than men. Whereas the repetition of driving sessions had no effect on men, the simulator sickness intensity strongly tended to increase through sessions in women. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.2.2. Influence of gender on Oculomotor discomfort, Disorientation and Nausea symptoms

The means computed in the two gender groups for each class of symptoms through the three different sessions are shown in Fig. 3.

In the SSQ0 session, there was no significant effect of Gender [$F(1,46) = .035$; $p = .69$; $d_r = .22$] but a significant effect of Symptom [$F(1,46) = 32.49$; $p < .001$], demonstrating that even before the experimental driving sessions, regardless of the gender, individuals reported more Oculomotor symptoms than Disorientation ($p < .001$; $\alpha crit = .025$; $d_r = 1.3$) and Nausea ($p < .001$; $\alpha crit = .017$; $d_r = .0.9$) symptoms (see Fig. 3a). Note that this effect was mainly due to individuals reporting a slight fatigue before the driving sessions which is an item only involved in the computation of oculomotor discomfort score (see Fig. 1a in Chaumillon et al. (submitted for publication)). Importantly, these differences between classes of symptoms were not dependent on the gender as revealed by the non-significant interaction between Gender and Symptoms factors [$F(1,46) = .29$; $p = .59$].

Following the first driving session (*i.e.* SSQ1; see Fig. 3b), the bootstrapped ANOVA showed a significant effect of Gender [$F(1,46) = 8.96$; $p = .004$; $d_r = .79$] and an effect of Symptoms [$F(1,46) = 6.57$; $p = .014$], but no interaction between Gender and Symptoms factors [$F(1,46) = 2.66$; $p = .17$]. This pattern of results confirms that men are far less sensitive to simulator sickness than women (see Fig. 2, middle panel). Contrary to what the participants reported in SSQ0 session, the results recorded in SSQ1 session evidenced that less Oculomotor discomfort was experienced compared to Disorientation ($p < .001$; $\alpha crit = .025$; $d_r = .11$) and Nausea symptoms ($p < .001$; $\alpha crit = .017$; $d_r = .1$). There was no significant difference between Disorientation and Nausea symptoms ($p = .25$; $\alpha crit = .05$; $d_r = .02$). Interestingly, the breakdown of the non-significant interaction between the two factors strongly tended to show that the difference between women and men was expressed in Disorientation ($p = .029$; $\alpha crit = .008$; $d_r = .84$) and Nausea ($p = .027$; $\alpha crit = .006$; $d_r = .89$) symptoms but not in Oculomotor discomfort symptoms ($p = .15$; $\alpha crit = .01$; $d_r = .64$). Finally, whereas women were more affected by Disorientation symptoms compared to Oculomotor discomfort ($p = .029$; $\alpha crit = .007$; $d_r = .34$) and Nausea ($p = .003$; $\alpha crit = .0055$; $d_r = .21$) symptoms, men evidenced no significant difference between the three symptoms (all $p > .3$; see also Fig. 2a in Chaumillon et al. (submitted for publication)).

Statistical results obtained after the second driving session (*i.e. SSQ2*) indicated a significant effect of Gender [$F(1,46) = 9.08$; $p = .002$; $d_r = 1.04$], a significant effect of Symptoms [$F(1,46) = 5.05$; $p = .008$] as well as an interaction between these two factors [$F(1,46) = 2.71$; $p = .035$]. The breakdown of the factor Symptom revealed that Disorientation symptoms was significantly greater than Nausea ($p < .001$; $\alpha crit = .017$; $d_r = .12$) and Oculomotor symptoms ($p < .001$; $\alpha crit = .025$; $d_r = .11$) and that Nausea symptoms tended to be greater than Oculomotor symptoms ($p = .052$; $\alpha crit = .05$; $d_r = .08$). Nevertheless, the

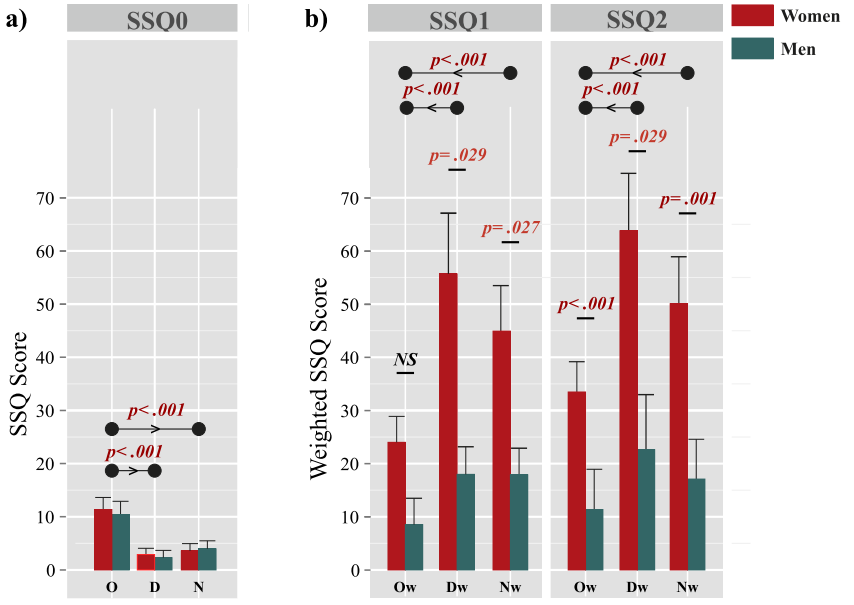

Fig. 3. Means of the three subclasses of symptoms computed in the two groups for each Simulator Sickness Questionnaire (SSQ) session. (a) Before the first driving session (*i.e.* SSQ0), women (red bars) as well as men (green bars) reported more oculomotor (O) symptoms than disorientation (D) and nausea (N) symptoms. This difference between symptoms is mainly due to individuals reporting a slight fatigue which is an item only involved in the computation of oculomotor discomfort score. (b) Statistical analyses performed after the driving sessions, demonstrated that less Oculomotor symptoms (Ow) were actually experienced compared to Disorientation (Dw) and Nausea (Nw) symptoms. Women demonstrated greater simulator sickness than men and this statement strongly tended to be observed in the three subclasses of symptoms. Red *p*-values show significant values after Hochberg's correction for multiple comparisons whereas orange *p*-values show values inferior to an alpha threshold of .05 but not inferior to *the critical alpha threshold* defined by Hochberg's correction for multiple comparisons. NS corresponds to a non-significant difference. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

breakdown of the significant interaction between the two factors revealed that these differences in susceptibility to symptoms were only due to the contribution of female participants. Indeed, women exhibited greater Disorientation symptoms than Nausea ($p = .008$; $\alpha crit = .008$; $d_r = .24$) and Oculomotor ($p < .001$; $\alpha crit = .0063$; $d_r = .4$) symptoms whereas men showed no significant differences between the three symptoms (all $p > .25$). Importantly, the pairwise multiple comparisons showed that the difference between women and men was strongly expressed in the Oculomotor ($p < .001$; $\alpha crit = .0055$; $d_r = 1.04$) and Nausea symptoms ($p = .001$; $\alpha crit = .007$; $d_r = 0.92$) and with a lesser extent in Disorientation symptoms ($p = .029$; $\alpha crit = .01$; $d_r = 1.15$; see also Fig. 2b in Chaumillon et al. (submitted for publication)).

2.3. Discussion

Large gender differences in susceptibility to simulator sickness were previously observed in fixed-based simulator studies (Garcia et al., 2010; Matas et al., 2015; Mourant & Thattacherry, 2000; Park et al., 2006; Park et al., 2008; Yoo, 1999). As stated in the introduction, we expected that simulator sickness and thus gender differences in susceptibility to simulator sickness would be reduced when participants were engaged in a driving task within a more realistic device. By demonstrating that women are far more likely to report simulator sickness than men while performing a driving task within a high-fidelity motion-based simulator, the present results did not support this assumption.

Considering previous studies in which total SSQ scores were available (*e.g.* Garcia et al., 2010; Park et al., 2006; Park et al., 2008), it seems that our motion-based driving simulator induces more simulator sickness than fixed-base simulators. For instance, Garcia et al. (2010) reported total SSQ scores of 16.36 ± 7.96 in men and 47.22 ± 7.90 in women when participants were tested within a fixed-base stimulator. We report in our study a total SSQ score of 23.38 ± 5.29 in men and 52.2 ± 8.23 in women after the first driving session and of 25.71 ± 7.93 in men and 61.08 ± 8.51 in women after the second driving session. Nevertheless, it should be recalled that contrary to Garcia et al. (2010) we used a scenario involving many turns and transient stops specifically designed to quickly induce simulator sickness.

Our results suggest that motion-based driving simulator would not be an effective way of reducing simulator sickness. Such a result reinforces Dziuda et al. (2014) conclusions. These authors argued that the mismatch between the true motion of the vehicle and the motion produced by simulator actuators might be responsible for the higher simulator sickness observed when individuals were engaged in a motion-based simulator. In our view, one plausible explanation comes from the characteristic of the motion system that we used. Considering the axis of motion installed on the VS500M car driving simulator, the vestibular system of participants conveyed vestibular feedback concerning linear acceleration but not angular acceleration during the driving sessions. The sensory conflict theory of simulator sickness obviously includes inter-sensory conflicts but also intra-sensory conflicts such as "*intra-vestibular conflicts between rotational accelerations sensed by the semicircular canals and linear-translational accelerations (including gravitational) sensed by the otoliths*". (Golding, 2006). Thus, when only linear-translational accelerations are available, as with our motion-based simulator, the intra-vestibular conflict could be increased and elicit simulator sickness higher in intensity. Finally, the fact that our motion-based simulator failed to reduce the simulator sickness felt by participants relative to fixed-base simulators suggests that the incongruence between expected and sensed angular acceleration cues might be critical in the pathogenesis of simulator sickness.

In 2008, Park et al., using a driving graphic simulator, showed that during a long driving session (*i.e.* 60 min) the level of simulator sickness increased linearly (see also Min, Chung, Min, & Sakamoto, 2004). These authors used the same scoring as that of the present study to assess simulator sickness intensity (*i.e.* SSQ) but were not concerned with potential gender differences in susceptibility to simulator sickness. Albeit the present experiment was of shorter duration (*i.e.* approximately 32 min in two separate driving sessions), the results demonstrated that the relationship between time and simulator sickness severity highlighted by this previous study actually holds only in women (see Fig. 1). This result adds an important consideration to the understanding of gender differences in susceptibility to simulator sickness which has never been addressed until now: the longer the exposure, the greater the difference between women and men widens.

Another result that might provide a better understanding of the causes of gender differences is the presence of statistical differences between the three classes of symptoms in women and their absence in men. Women were more likely to report disorientation symptoms than oculomotor and nausea symptoms. Despite no straight statistical comparison being available, graphical exploration of the results from previous studies indicates that, irrespective of gender, the higher likelihood to report disorientation rather than oculomotor and nausea symptoms seems to be a common observation (Dziuda et al., 2014; Garcia et al., 2010; Park et al., 2006, *dropout group*; Park et al., 2008; Stanney & Kennedy, 1998 but see Mourant & Thattacherry, 2000 *and non-dropout group in* Park et al., 2006).

In sum, the present results provide important insights toward a better understanding of gender differences in susceptibility to simulator sickness. Unexpectedly, the present results also show that gender differences still remain, to the same extent, even when the congruence between visual, somatosensory and vestibular motion cues is widely improved. Consequently, searching for new methods of reducing gender differences in susceptibility to simulator sickness in order to preserve representative participation by various subgroups within the population remains a core need. With this aim in view, we conducted a second experiment in which we assessed the effectiveness of transdermal scopolamine as a preventive treatment of simulator sickness induced by our motion-based driving simulator.

3. Experiment 2: Scopolamine's influence on gender differences in susceptibility to simulator sickness

3.1. Material and methods

3.1.1. Participants

One third of the forty-eight participants involved in **experiment 1** performed a second experiment focusing on the role of the scopolamine. We investigated whether scopolamine, a substance known to effectively prevent the symptoms of motion sickness (*e.g.* Uijtdehaage, Stern, & Koch, 1993), could be efficient to cancel the gender difference in susceptibility to simulator sickness. In this study, the sixteen participants were classified in two experimental groups depending on their gender: 7 women (mean age ± SD = 23 ± 1.8 years old) and 9 men (mean age ± SD = 24.6 ± 3.2 years old).

We used the exact same Simulator Sickness Questionnaire (SSQ) and experimental setup as in the **experiment 1** (see Sections 2.1.2 and 2.1.3).

3.1.2. Task and protocols

In this study, the experimental design comprised two experimental sessions performed in two distinct days separated from each other by a week. One session, hereafter called Control condition, was performed under the placebo influence whereas the other session, hereafter called Scopolamine condition, was performed under scopolamine influence. During these two sessions, the task and protocol (*i.e.* experimental time course: SSQ0 – first driving session – SSQ1 – second driving session – SSQ2) were strictly identical as those detailed in **experiment 1** (see **part 2.1.4.**). The only difference between the two experimental sessions was the type of medication (*i.e.* placebo or scopolamine) that participants received 12 h before the session. This experimentation was run in counterbalanced between subjects order and conducted in a double-blind design. Indeed, the medical supervisor administered the scopolamine in the first experimental session to eight participants and the placebo in the first experimental session to the eight others and was the only one among the authors to know in which conditions the participants were engaged. Note that participants' results obtained in the Placebo condition are embedded in those presented in the **experiment 1.**

3.1.3. Transdermal scopolamine (TransdermV®) administration

A comparative study demonstrated that incidence and intensity of the side effects following a scopolamine administration were dependent on the delivery method (Nachum et al., 2006; Spinks & Wasiak, 2011). They evidenced lower incidence after transdermal administration compared to oral or intravenous administration. Additionally, transdermal administration has been widely used and repeatedly shown its efficiency in preventing seasickness (Attias, Gordon, Ribak, Binah, & Rolnick, 1987; Laitinen, Tokola, Gothoni, & Vapaatalo, 1981; Price, Schmitt, McGuire, Shaw, & Trobough, 1981; Tokola, Laitinen, Aho, Gothoni, & Vapaatalo, 1984) and motion sickness (Gordon et al., 2001; Nachum et al., 2006; Uijtdehaage et al., 1993). Consequently, transdermal scopolamine seemed to be the best option.

The protocol of scopolamine administration took place under the supervision of Dr. Jean-François Bouchard, pharmacist and member of the Quebec College of Pharmacists. Twelve hours before each of the two experimental sessions, either a placebo patch or a transdermal scopolamine patch (Transderm-V® 1.5 mg marketed by Novartis Pharma®), was placed on post-auricular skin of the participant. This time delay between administration and experimentation was chosen because the maximal blood concentrations of the substance are classically obtained approximately 12 h after the patch installation (see the comprehensive review from Nachum et al., 2006). The patch is designed to liberate 140 μg of scopolamine as a priming dose and to deliver 1 mg of scopolamine at a constant rate during its active period of 72 h (Nachum et al., 2006). This administration mode has the advantage of producing a predictable and precise plasma concentration (Nachum et al., 2006). Participants were controlled to exclude contraindications (*e.g.* pressure pain, blurred vision, glaucomatous halo) and were monitored throughout the experimentation by Dr Bouchard. Participants were informed that they had the possibility to drop out the experimentation at any time without penalty.

3.1.4. Statistical analysis

We assessed the effectiveness of transdermal scopolamine as preventive treatment of simulator sickness induced by a driving simulator. Consistent with the differences between women and men in susceptibility to simulator sickness that we previously observed (**Experiment 1**), we were interested by the potential interaction between gender and scopolamine influence on simulator sickness in the present study. With this aim in view, the SSQ scores were submitted to a between (Gender: Women; Men) by within (Conditions: Control; Scopolamine) by within (SSQ_session: SSQ0; SSQ1; SSQ2) bootstrapped ANOVA with repeated measures on the last two factors. Once again, it appeared relevant to perform subsequent separate analyses for each of the three sessions to investigate the cross-effect of scopolamine administration and gender on the three symptoms considered in the SSQ score computation. As in **experiment 1**, the use of separate analyses for each session stressed the need to correct the SSQ scores obtained in SSQ1 and SSQ2 with the "basal threshold" (i.e. SSQ0) from each subject. Separately for each of the three sessions, these weighted scores were submitted to a between (Gender: Women, Men) by within (Condition: Control, Scopolamine) by within (Symptoms: Oculomotor discomfort [Ow], Disorientation [Dw], Nausea [Nw]) bootstrapped ANOVA.

3.2. Results

3.2.1. Effects of scopolamine and gender in susceptibility to simulator sickness

Means of the SSQ scores obtained in each Group and each Condition through the three different SSQ sessions are shown on the Fig. 4. SSQ scores were submitted to a between (Gender: Women; Men) by within (Condition: Control; Scopolamine) by within (SSQ_session: SSQ0; SSQ1; SSQ2) bootstrapped ANOVA. It revealed a significant effect of factor Condition [$F(1,14) = 8.36$; $p = .005$; $d_r = .76$] demonstrating that simulator sickness was significantly less intense in scopolamine than in control condition. From a quantitative point of view, total SSQ1 and SSQ2 scores, computed over the 16 participants in control condition were respectively reduced by 66.5% and 64.6% after scopolamine administration.

Statistical analysis showed a marginal but non-significant effect of Gender [$F(1,14) = 3.79$; $p = .072$; $d_r = 1.26$]. This absence of gender effect is not in line with our previous observations (**experiment 1**). The reason for falling just short of the conventional .05 cut-off value for statistical significance could be found by analyzing the non-significant interaction between Gender and Condition factors [$F(1,14) = .81$; $p = .37$]. Indeed, the multiple comparisons performed on the interaction between these two factors revealed that women experienced greater simulator sickness than men in control condition ($p = .006$; $\alpha crit = .025$; $d_r = 1.04$) but not in scopolamine condition ($p = .26$; $\alpha crit = .05$; $d_r = .42$). Thus, it appears, that scopolamine administration allows the drastic reduction of gender differences in susceptibility to simulator sickness experienced in a motion-based simulator.

A main effect of factor SSQ session [$F(1,14) = 22.09$; $p = .012$] showing that SSQ scores were overall different between the three sessions has been evidenced. The multiple pairwise comparisons performed on the SSQ session factor showed that SSQ0 scores were significantly lower than SSQ1 ($p < .001$; $\alpha crit = .025$; $d_r = .1.75$) and SSQ2 ($p < .001$; $\alpha crit = .017$; $d_r = .1.83$) scores, whereas SSQ1 and SSQ2 scores were not statistically different ($p = .31$; $\alpha crit = .05$; $d_r = .04$). Additionally, the breakdown of the significant interaction between Condition and SSQ session factors [$F(1,14) = 8.58$; $p = .033$] evidenced that SSQ1 and SSQ2 scores registered in scopolamine condition were each significantly lower compared to SSQ1 ($p < .001$; $\alpha crit = .007$; $d_r = .63$) and SSQ2 ($p = .002$; $\alpha crit = .013$; $d_r = .68$) scores observed in the control condition. There was no statistical difference between SSQ0 scores recorded in the control condition and those recorded in the scopolamine condition ($p = .48$; $\alpha crit = .05$; $d_r = .21$). This result demonstrates that individuals were not affected by the potential side effects following a scopolamine administration before the driving sessions. When considering each condition separately, it appeared that SSQ0 scores were significantly lower than SSQ1 ($p < .001$; $\alpha crit = .01$; $d_r = 1.21$) and SSQ2 ($p = .002$; $\alpha crit = .0083$; $d_r = 1.48$) scores in the control condition, as well as in the scopolamine condition [SSQ0 vs SSQ1 ($p < .001$; $\alpha crit = .0063$; $d_r = 1.68$); SSQ0 vs SSQ2 ($p < .001$; $\alpha crit = .0055$; $d_r = 1.33$)]. This pattern of results evidenced that simulator sickness was indeed strongly restricted but not totally suppressed following the scopolamine administration.

Finally, there were no significant interaction between Gender and Sessions factors [$F(1,14) = 1.9$; $p = .19$] and no second-order interaction between the three factors [$F(1,14) = .23$; $p = .3$].

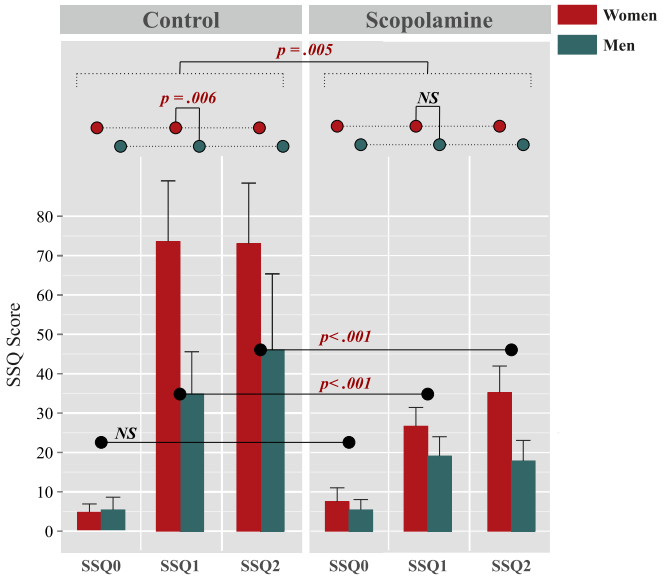

Fig. 4. Means of the total SSQ scores obtained in women and men within the two experimental conditions. The statistical analysis revealed that SSQ scores were significantly higher in control (left panel) than in scopolamine condition (right panel; $p = 0.005$). Multiple pairwise analyses showed that this statement held in SSQ1 ($p < 0.001$) as well as in SSQ2 ($p < 0.001$). The two SSQ sessions performed before the driving sessions (i.e. SSQ0 in control and in scopolamine conditions) were logically not statistically different ($p = 0.31$). The significant gender difference in control condition ($p = 0.006$) and its absence in scopolamine condition ($p = 0.26$) evidenced that scopolamine administration is an efficient tool to decrease gender differences in susceptibility to simulator sickness.

3.2.2. Effects of scopolamine and gender on the three symptoms classified in the SSQ

For each of the three SSQ sessions, separate between (Gender: Women, Men) by within (Condition: Control, Scopolamine) by within (Symptoms: Oculomotor discomfort, Disorientation, Nausea) bootstrapped ANOVA was performed.

In the SSQ0 session, it resulted in no significant effect of Gender [$F(1,14) = .004$; $p = .95$; $d_r = .05$] and no effect of Condition [$F(1,14) = .56$; $p = .47$; $d_r = .2$]. Unexpectedly, there was a significant effect of Symptom [$F(1,14) = 14.44$; $p = .002$], demonstrating that even before the experimental driving sessions, regardless of gender, individuals thought that they would be more sensitive to Oculomotor symptoms than to Disorientation ($p < .001$; $\alpha crit = .025$; $d_r = .65$) and Nausea ($p < .001$; $\alpha crit = .017$; $d_r = .9$) symptoms (see Fig. 5a). This effect was, once again, mainly due to individuals reporting a slight fatigue before the driving sessions which is an item only involved in the computation of oculomotor discomfort score (see Fig. 1b in Chaumillon et al. (submitted for publication)). These differences between classes of symptoms were not dependent on the gender nor on the condition as revealed by the non-significant first and second-order interactions (all $F < 2$; all $p > .1$).

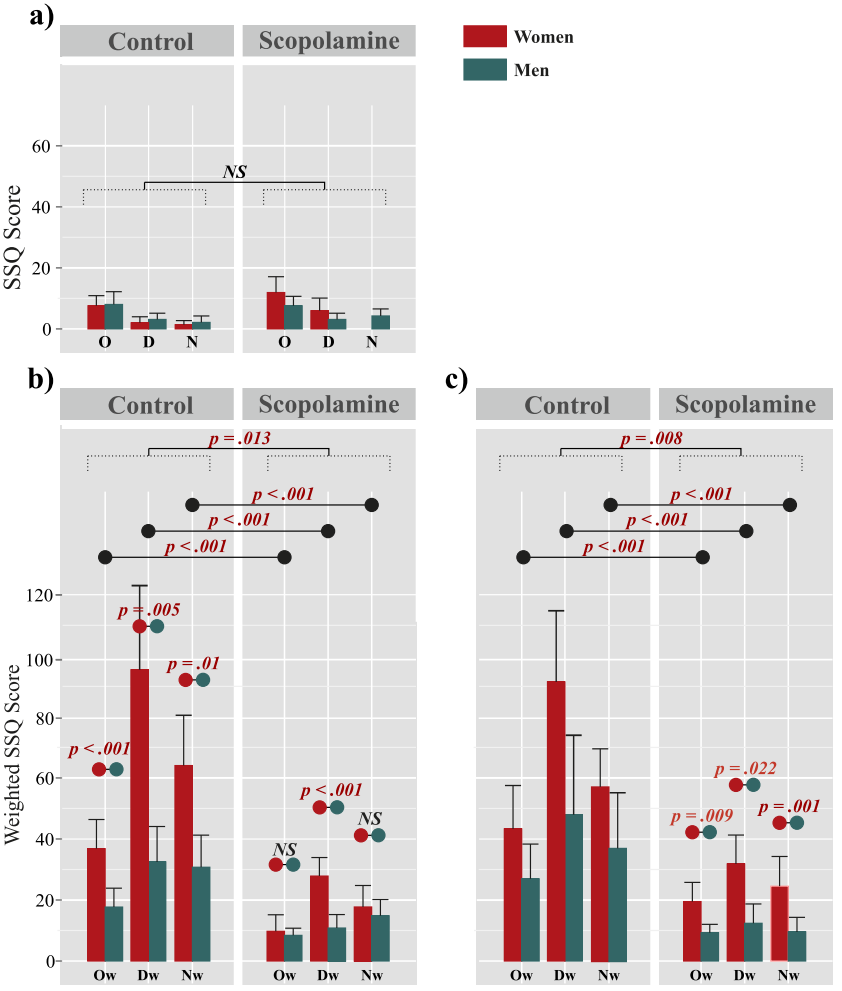

Fig. 5. Means of the three subclasses of symptoms computed in the two groups for each condition (Control; Scopolamine) and each Simulator Sickness Questionnaire (SSQ) session. (a) Even before the first driving session (i.e. SSQ0), women (red bars) as well as men (green bars) reported more oculomotor (O) symptoms than disorientation (D) and nausea (N) symptoms. This difference between symptoms is mainly due to individuals reporting a slight fatigue which is an item only involved in the computation of oculomotor discomfort score. Importantly, there were no gender nor condition effects before the driving sessions. (b) Statistical analysis performed over the symptom scores recorded after the first driving session (i.e. SSQ1) evidenced that scopolamine administration resulted in significantly reduced oculomotor discomfort (Ow; $p < 0.001$), disorientation (Dw; $p < 0.001$) as well as nausea (Nw; $p < 0.001$) symptoms. Additionally, the significant gender differences observed in Oculomotor ($p < 0.001$) and Nausea symptoms ($p = 0.01$) during the control condition and their absence (Ow: $p = 0.86$; Nw: $p = 0.61$) during the scopolamine condition evidenced that transdermal scopolamine is an efficient tool in reducing gender differences in susceptibility to simulator sickness. (c) An identical large decrease in symptom intensity following scopolamine administration was observed after the second driving session [Ow: $p < 0.001$; Dw: $p < 0.001$; Nw: $p < 0.001$]. Nevertheless, contrary to SSQ1, gender differences tended to be observed in the three symptoms during the scopolamine condition (Ow: $p = 0.009$; Dw: $p = 0.022$; Nw: $p = 0.001$). The reappearance of these gender differences after the second exposure to the driving simulator raises the question of the scopolamine effectiveness over time. Red *p*-values show significant values after Hochberg's correction for multiple comparisons whereas orange *p*-values show values inferior to .05 but not inferior to the *critical alpha threshold* defined by Hochberg's correction for multiple comparisons. NS corresponds to a nonsignificant difference.

After the first driving session (*i.e.* SSQ1; see Fig. 5b), the bootstrapped ANOVA revealed a non-significant trend of an effect of Gender [$F(1,14) = 4.8$; $p = .07$; $d_r = 1.05$], a significant effect of Condition [$F(1,14) = 15.78$; $p = .013$; $d_r = .6$] and no interaction between these two factors [$F(1,14) = 3.97$; $p = .11$]. This pattern of results strongly strengthens our preceding observations (see **part 3.2.1.**). More interestingly for the present purpose, there was also an effect of Symptoms [$F(1,14) = 10.87$; $p = .035$]. The breakdown performed on this factor revealed that, irrespective of their gender and experimental condition, participants were more likely to report disorientation than oculomotor symptoms ($p < .001$; $\alpha crit = .017$; $d_r = .52$) and with a lesser extent than nausea symptoms (p = .052; $\alpha crit = .05$; $d_r = .08$). At the same time, participants were more likely to report nausea than oculomotor symptoms ($p = .002$; $\alpha crit = .025$; $d_r = .77$) giving rise to a clear classification of symptoms: Disorientation > Nausea > Oculomotor discomfort.

An important point to consider is that the multiple pairwise comparisons performed on the non-significant interaction between Condition and Symptom factors [$F(1,14) = 2.28$; $p = .19$] demonstrated that the scopolamine administration was sufficient to reduce all three symptoms: for each symptom, we noted a large reduction of simulator sickness between the two conditions [Oculomotor discomfort (−65.5%; $p < .001$; $\alpha crit = .0063$; $d_r = .65$); Disorientation (−69.6%; $p < .001$; $\alpha crit = .0056$; $d_r = .58$); Nausea (-64.5%; $p < .001$; $\alpha crit = .0071$; $d_r = .81$)]. Moreover, the scopolamine administration significantly reduced gender differences in susceptibility to simulator sickness. Indeed, as revealed by the multiple pairwise comparisons of the non-significant second-order interaction [$F(1,14) = .54$; $p = .54$], gender differences were observed in Oculomotor ($p < .001$; $\alpha crit = .0056$; $d_r = .81$), Disorientation ($p = .005$; $\alpha crit = .006$; $d_r = .93$) and Nausea ($p = .01$; $\alpha crit = .013$; $d_r = .97$) symptoms in the control condition whereas we observed them only in Disorientation symptoms during the scopolamine condition [Dw ($p < .001$; $\alpha crit = .0056$; $d_r = .1.21$); Ow ($p = .86$; $\alpha crit = .025$; $d_r = .03$); Nw ($p = .61$; $\alpha crit = .013$; $d_r = .14$)]. Finally, another interesting effect of scopolamine administration is that it cancelled differences between various symptoms: whereas women exhibited greater Disorientation than Oculomotor ($p = .008$; $\alpha crit = .01$; $d_r = .1.32$) and Nausea ($p = .008$; $\alpha crit = .0083$; $d_r = .71$) symptoms in control condition, they showed neither differences between Disorientation and Oculomotor ($p = .03$; $\alpha crit = .006$; $d_r = .36$) symptoms, between Disorientation and Nausea ($p = .09$; $\alpha crit = .0071$; $d_r = .46$) symptoms, nor between Oculomotor and Nausea ($p = .31$; $\alpha crit = .008$; $d_r = .57$) symptoms in scopolamine condition.

Similarly to SSQ1, the statistical analysis performed on SSQ2 scores (Fig. 5c) evidenced no effect of Gender [$F(1,14) = 1.99$; $p = .175$; $d_r = 1.56$], a strong effect of Condition [$F(1,14) = 8.76$; $p = .008$; $d_r = .61$] and no interaction between these two factors [$F(1,14) = .28$; $p = .58$]. This pattern of results reinforces the claim that scopolamine administration is a good tool to reduce simulator sickness as well as gender differences in susceptibility to simulator sickness. There was also a significant effect of Symptom [$F(1,14) = 3.11$; $p = .029$] evidencing the same classification of symptoms as during the first driving session [*i.e.* Disorientation > Nausea > Oculomotor discomfort; Dw vs Nw ($p = .014$; $\alpha crit = .025$; $d_r = .21$); Dw vs Ow ($p < .001$; $\alpha crit = .017$; $d_r = .45$); Nw vs Ow ($p = .04$; $\alpha crit = .05$; $d_r = .32$)] and a strong trend toward an interaction between Condition and Symptom factors [$F(1,14) = 1.98$; $p = .061$]. Multiple pairwise comparisons performed on this interaction revealed that scopolamine administration was sufficient to reduce the three classes of symptoms [Oculomotor discomfort (−59.7%; $p < .001$; $\alpha crit = .0071$; $d_r = .62$); Disorientation (-68.8%; $p < .001$; $\alpha crit = .0063$; $d_r = .56$); Nausea (−64.9%; $p < .001$; $\alpha crit = .0056$; $d_r = .83$)].

Notwithstanding these undeniable positive effects of scopolamine and a clear graphic likeness between SSQ1 and SSQ2 results (see Fig. 5b and c), the breakdown of the non-significant second-order interaction [$F(1,14) = .005$; $p = .58$] revealed a lower effectiveness of transdermal scopolamine in reducing gender differences in susceptibility to simulator sickness during the second driving session. Indeed, when considering the scopolamine condition, gender differences were only observed in Disorientation symptom after the first driving session, whereas they were observed in Nausea symptom ($p = .001$; $\alpha crit = .0056$; $d_r = .63$) and to a lesser extent in Oculomotor ($p = .009$; $\alpha crit = .0071$; $d_r = .79$) and Disorientation symptoms ($p = .022$; $\alpha crit = .0083$; $d_r = .99$) after the second driving session. Thus, it appears that scopolamine efficiency in reducing gender differences in susceptibility to simulator sickness may depend on the duration of exposure to driving simulator.

3.3. Discussion

Two main results stand out from the present experiment. Firstly, the transdermal scopolamine is an effective tool to drastically decrease simulator sickness related to motion-based driving simulator. The total SSQ score observed in the scopolamine condition was decreased by 60% compared to that observed in the control condition. This result is in line with previous studies demonstrating the effectiveness of transdermal scopolamine in motion sickness (Gordon et al., 2001; Nachum et al., 2006) and further supports the attention that should be paid to this drug. Importantly, statistical comparisons between the three classes of symptoms brought into focus that the effects of scopolamine are not specific to only one class of symptoms but instead efficiently acts on each class of symptoms to the same extent (*i.e.* oculomotor discomfort, disorientation and nausea). Secondly, transdermal scopolamine allows the temporary cancellation of gender differences in susceptibility to simulator sickness. In our view, this latter result is of critical importance for methodological considerations and paves the way toward wider and better-controlled experimental possibilities.

Simulator sickness was not completely removed following the transdermal scopolamine administration. Indeed, we observed a drastic decrease in the severity of symptoms but a residual unease still remained. A plausible explanation comes from studies in patients with bilateral vestibular loss (BVL). Indeed, Golding and Gresty (2013), demonstrated that patients with BVL are, surely, highly resistant to motion sickness but that several patients can still exhibit some degree of motion sickness. These authors claimed that other types of sensory conflict coming from inputs other than vestibular ones might

be responsible for these remaining symptoms of motion sickness in patients with BVL (Golding & Gresty, 2013; Golding & Gresty, 2015). In the same way, the scopolamine – which acts as an inhibitor of vestibular motion cues – might suppress vestibular conflict but should be useless in resolving the other types of sensory conflicts.

Although the difference was not significant, total SSQ score tended to be higher after the second than after the first driving session in the scopolamine condition (Fig. 4). Moreover, gender differences in susceptibility to simulator sickness were statistically cancelled after SSQ1 but tended to resurface after the second driving session (Figs. 4 and 5b and c). Together, these results indicate that scopolamine's efficiency may depend on the duration of exposure to the driving simulator. Because a wide corpus of studies demonstrated the long-lasting prophylactic effect of transdermal scopolamine (Zhang et al., 2016 for a recent review) a hypothetical diminution of drug efficiency is excluded from consideration. It would be more relevant to consider the well-known increasing in simulator sickness over time (Min et al., 2004; Park et al., 2008, Experiment 1 of the present study). Studies demonstrating this effect used the SSQ scores to quantify simulator sickness, evidenced a significant increase of scores over time in the three classes of symptoms, but none of them performed analysis on individual item score elevation. However, it has been recently suggested that the segregation of SSQ scores into three classes of symptoms might be too limited to accurately assess severity in simulator sickness (Balk et al., 2013). Indeed, these authors performed a factor analysis based on SSQ scores coming from nine studies performed on driving simulators. Although their factor analysis resulted in the same three orthogonal classes of symptoms as Kennedy et al. (1993), unlike this pioneering study, no items were attributed to more than one factor and five items were not attributed to any class of symptoms. As a result, they claimed that an exploration of each item score should give additional cues on individual profiles.

We performed such an individual item score analysis in assessing the elevation between SSQ1 and SSQ2 scores in each of the sixteen symptoms during the scopolamine condition (see Fig. 6). It revealed that gender differences in the amount of increase was particularly marked in the fatigue item and to a lesser extent in the eyestrain item. At first sight, there is no reason to think that scopolamine could have a direct influence on oculomotor symptoms such as fatigue and eyestrain. Consequently, the slight increase in simulator sickness after the second driving session might be linked to a normal visual fatigue driven by any experimental protocol involving sustained and repeated visual stimuli (*e.g.* Arsalan Naqvi et al., 2015; Solimini, 2013). Moreover, two recent studies from ergonomics and ocular disease prevention domains, suggested that women are more likely to report visual fatigue symptoms than men (Porcar, Pons, & Lorente, 2016; Toomingas et al., 2014). Thus, potential gender differences in visual fatigue are more likely to be responsible for the resurfacing gender differences in susceptibility to simulator sickness than potential differences in long-term robustness to drug assimilation.

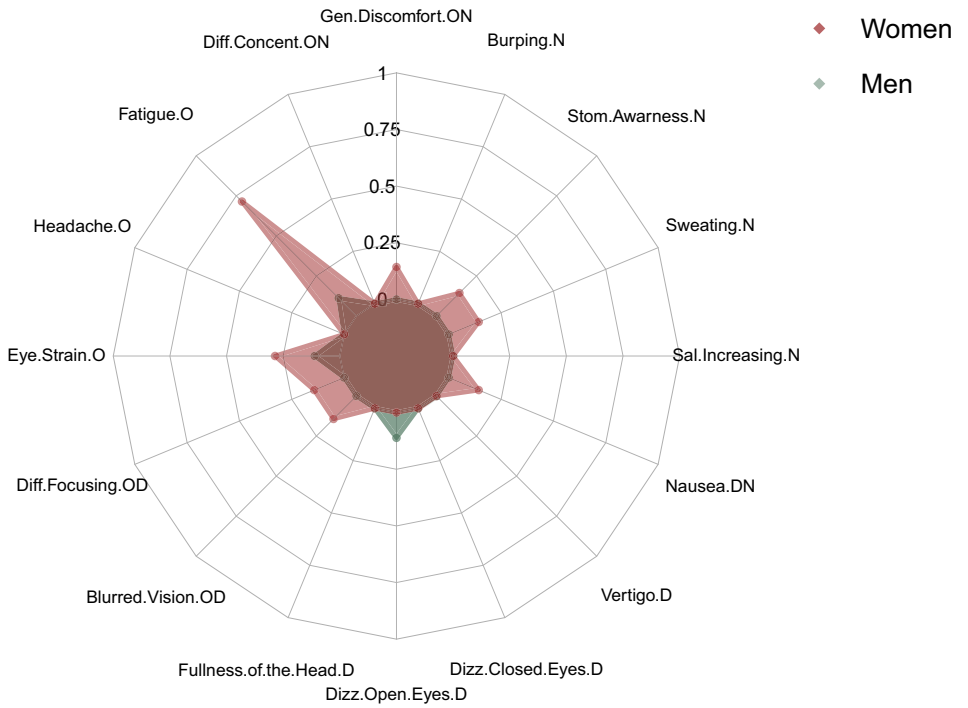

Fig. 6. Mean item score elevation between SSQ1 and SSQ2 in the scopolamine condition. The oculomotor symptoms and, specifically, the fatigue and eyestrain items show a higher increase between SSQ1 and SSQ2 under the scopolamine condition in women (red area) than in men (green area). This pattern of results suggests that oculomotor symptoms are mainly responsible for the resurfacing gender differences observed in SSQ2 session under scopolamine condition. The O, D and N letters following the name of each item indicate in which class(es) of symptoms the corresponding item was involved. With O corresponding to Oculomotor discomfort, D to Disorientation and N to Nausea.

Like any other drug, transdermal scopolamine entails side effects. In the present study, 10 among 16 participants indicated dryness of the mouth and 2 among 16 participants reported drowsiness. These symptoms are commonly reported following scopolamine administration (Brainard & Gresham, 2014; Nachum et al., 2006) and should be considered as having limited impact on the natural behavior of participants. Indeed, concerning the former, its inability to affect the natural behavior of the participants is manifest. Concerning the latter, a large set of studies established that this feeling was actually increased during passive phases of the experimentation but not under the stress of active experimental phases (Dahl, Offer-Ohlsen, Lillevold, & Sandvik, 1984; Gordon, Binah, Attias, & Rolnick, 1986; Gordon et al., 2001; Parrott, 1987).

Beyond these side effects, drugs can also have adverse effects on performances (Lucot, 1998). Thus, it is of critical importance to determine whether the benefit provided by the drug is worth the side effect costs. Several central nervous system functions are subserved by acetylcholine neurotransmission, including the maintenance of attention and vigilance and the integrity of alertness or arousal (Nachum et al., 2006; Warburton & Wesnes, 1984). Consequently, the question of the impairment of these functions under scopolamine influence is a major concern. Nevertheless, it was shown that contrary to oral and parental administration (Parrott, 1986; Parrott, 1987; Parrott, 1989), transdermal administration did not impair psychomotor skills, response speed, and cognitive information processing (Gordon et al., 1986; Gordon et al., 2001; Howland et al., 2008; Parrott, 1989). Moreover, it was recently shown that attentional processes are also unaffected by low doses of scopolamine administration (Bestaven, Kambrun, Guehl, Cazalets, & Guillaud, 2016). From a methodological point of view, the results of the present experiment coupled with these previous studies indicate that transdermal scopolamine has greater positive than negative impact on the assessment of natural driving abilities. Notwithstanding these results, further studies should investigate more deeply whether higher-level cognitive tasks such as those specifically involved in driving (*e.g.* divided attention, multiple object tracking) are impaired following transdermal scopolamine administration.

4. General discussion

While car driving simulators are an essential research tool for assessing drivers' behavior under safe and controlled conditions, it appears that experimental conditions, effect reliability and recorded measures are strongly hampered by individual differences in susceptibility to simulator sickness (Classen et al., 2011; Helland et al., 2016). The present experiment aimed to assess the efficiency of one technological (the use of high-fidelity motion-based driving simulator) and one pharmacological solution (the use of transdermal scopolamine) to solve the methodological issues raised by gender differences in susceptibility to simulator sickness. The results showed that the pharmacological but not the technological solution was effective in limiting these methodological issues. By bringing a new tool allowing to control gender differences, the use of transdermal scopolamine is an important step toward a more accurate assessment of driving abilities through driving simulators

Considering the well-proven effectiveness of driving simulators in many fields (see Matas et al., 2015 for an extensive review) and the fact that these tools are increasingly accessible to researchers and therapists, there is a strong practical motivation to gain a better understanding of the underlying causes of simulator sickness. The second experiment evidenced that transdermal scopolamine can be used to resolve methodological issues raised by gender differences in susceptibility to simulator sickness and therefore sheds new light on the mechanisms underlying these differences. Previous attempts to explain gender differences mainly focused on sociological, hormonal and psychological factors. For instance, Klosterhalfen et al. (2005) proposed that gender differences in susceptibility to motion sickness would be due, at least a part, to social or gender-role issues: women might be more likely than men to admit aversive subjective symptoms. Howarth and Griffin (2003) suggested that female hormonal cycles might be responsible for gender difference and Paillard et al. (2013) attempted to link the higher anxiety level observed in women to their higher susceptibility to motion sickness. By demonstrating that scopolamine annihilates gender differences, the results of the present experiment reinforce the already substantial list of evidence against these explanatory theories (see Golding, 2006). Indeed scopolamine cannot have an impact on social stereotypes and is not known to induce significant hormonal changes or modulation of anxiety. Moreover, albeit that personality traits and more specifically anxiety may be a potentially influential factor on questionnaire completion (Collins & Lentz, 1997; Kim, Kim, Kim, Ko, & Kim, 2005), our protocol allowed to minimize the potential influence of participant's willingness to report their symptoms. Indeed, each participant filled a Simulator Sickness Questionnaire before the first driving session (*i.e.* SSQ0) to obtain an individual "basal threshold". Therefore, in statistical analyses, participants were their own reference and SSQ scores obtained should only reflect the increase of symptoms due to the driving simulator immersion. In sum, identifying the mechanisms responsible for gender differences is beyond the scope of the study but our results offer the demonstration that its origins are more likely physiological/neurophysiological rather than sociological or psychological.

Interestingly, the analysis by item performed in the second experiment suggests that gender differences in susceptibility to simulator sickness observed through SSQ scores, might be linked, at least partially, to gender differences in eyestrain and general fatigue. Some studies from ergonomics and ocular disease prevention, have already raised the question of gender differences in susceptibility to eyestrain. For instance, Toomingas et al. (2014), showed that the incidence of eye-symptoms such as eyestrain among professional computer users depends on gender: women were more likely to report eye-symptoms than men. Recently, Porcar et al. (2016), comparing population of professional video display users, reported a significant higher proportion of eye-symptoms such as tired eyes in women than in men. Thus, gender differences in sus-

ceptibility to visual fatigue might be a confounding factor in simulator sickness assessment and has to be carefully considered in further studies.

Driving simulators are widely used to assess driving abilities in older people and people with visual impairments under various controlled laboratory conditions. Indeed, considering that driving is the principal mode of travel for adults in many countries (Hu & Reuscher, 2004) and that the demographic shift implies that we should see an ever growing proportion of older drivers, it is crucial to understand what factors are involved in the observed age-related decline in driving performance. Such information is of use to policy makers and can be acquired through driving simulator studies. Although the present results evidenced that transdermal scopolamine helps to more accurately study driving behavior in young people, it should be warned that the use of this drug in older populations may be further difficult if not dangerous. Indeed, several clinical studies reported cases of psychosis following scopolamine administration (Cairncross, 1983; MacEwan, Remick, & Noone, 1985; Osterholm & Camoriano, 1982) and showed that anticholinergic drugs as a whole may elicit sleepiness, memory lapses, urinary retention, and even delirium when used in older patients (Burke, 1995). Similarly, because scopolamine may cause an increase in intraocular pressure, its use is inappropriate in individuals predisposed to narrow-angle glaucoma (Renner et al., 2005). In these specific populations other alternatives must be sought.

5. Conclusion

In sum, our findings provide the first evidence that transdermal scopolamine can be used to resolve methodological issues raised by gender differences in susceptibility to simulator sickness. Because car driving is paramount to our daily-life and because driving simulators are an essential research tool for assessing drivers' behavior under safe and controlled conditions, controlling gender differences in experimental designs is of general importance at a societal level. As such, the use of transdermal scopolamine is a breakthrough to more accurately study driving abilities using driving simulators and paves the way toward wider and better-controlled experimental possibilities. The present results call for further investigations in order to study the long-term efficacy of transdermal scopolamine and whether more high-level cognitive tasks such as those specifically involved in driving task are impaired following transdermal scopolamine administration.

Funding

This research was supported by an NSERC-Essilor industrial research chair awarded to Jocelyn Faubert.

Declaration of interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to thank Jesse Michaels for English proof-reading as well as Carine Saint-Jalm and Sandy Michel for their help in data collection. We are also grateful for the insightful comments and recommendations provided by the two Reviewers.

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