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Self-adjustments may account for the contradictory correlations between HRV and motion-sickness severity

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A B S T R A C T

This study investigates the relationship between heart rate variability (HRV) and the level of motion sickness (MS) induced by simulated tunnel driving. The HRV indices, normalized low frequency (NLF, 0.04–0.15 Hz), normalized high frequency (NHF, 0.15–0.4 Hz), and LF/HF ratio were correlated with the subjectively and continuously rated MS levels of 20 participants. The experimental results showed that for 13 of the subjects, the MS levels positively correlated with the NLF and the LF/HF ratio and negatively correlated with the NHF. The remaining seven subjects had negative correlations between the MS levels and the NLF and the LF/HF ratio and a positive correlation between the MS levels and the NHF. To clarify this contradiction, this study also inspected the effects of subjects' self-adjustments on the correlations between the MS levels and the HRV indices and showed that the variations in the relationship might be attributed to the subjects' self-adjustments, which they used to relieve the discomfort of MS.

1. Introduction

Heart rate variability (HRV) is an oscillation in the interval between consecutive heartbeats, and this phenomenon is caused by the influence of the autonomic nervous system on the sinus node of the heart (Stauss, 2003). Power spectral analysis of the R–R interval time series is one of the most promising quantitative methods for assessing sympathovagal interactions (Stauss, 2003; Pagani et al., 1986; Parati et al., 2006). Three spectral components are identified in the power spectrum of R–R interval time series and constitute the HRV indices (3): very low frequency (VLF) (0.003–0.04 Hz), low frequency (LF) (0.04–0.15 Hz) and high frequency (HF) (0.15–0.4 Hz) components. The LF component of HRV is a joint action of the sympathetic and vagal activities on the heart that is predominantly under sympathetic influence (Casu et al., 2005), and the HF component is an indicator of vagal nerve activities (Beckers et al., 2006; Emoto et al., 2007; Stauss, 2003). The LF/HF ratio reflects the changes in sympathetic–parasympathetic activities and is typically used to characterize the sympathovagal balance of the heart (Demaree and Everhart, 2004; Wodey et al., 2003). The VLF component is less commonly used, and its physiological mechanism is not well-established (Camm et al., 1996; Kato et al., 2004).

Motion sickness (MS), a common experience for car, airplane, and sea passengers, can cause mild to severe discomfort. The symptoms of the MS include headache, eye strain, pallor, sweating, vertigo, ataxia, nausea, and vomiting. The occurrence, severity and duration of the MS symptoms are varied across individuals (Turner and Griffin, 1999). Several studies reported that the symptoms of MS can be deleteriousness to self-control and task performance. Therefore, numerous studies have attempted to determine the etiology of MS and the ideal methods to prevent the induction of MS or to relieve the discomfort of MS symptoms. Because MS symptoms are associated with perturbed sympathovagal activities, changes in the HRV indices have been used to assess the MS-induced perturbations in sympathetic activity and sympathovagal imbalance (Emoto, 2008; Emoto et al., 2007; Gianaros et al., 2003; Morrow et al., 2000; Ohyama et al., 2007; Yokota et al., 2005). However, whether the changes in the HRV indices can be directly correlated with MS severity remains uncertain. Some studies suggested that the changes in the HRV indices were related to the degree of MS

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(Gianaros et al., 2003; Holmes and Griffin, 2001; Yokota et al., 2005), but others reported that the HRV indices did not correlate with the MS levels (Beckers et al., 2006; Bos and Bles, 1998; Ohyama et al., 2007; Peng et al., 2007). The above discrepancies are possibly caused by differences in the methods used to induce MS and to assess the relationship between the MS levels and the HRV indices, as well as by the influence of uncontrolled self-adjustments during the MS induction.

MS induction is a consequence of conflicting perceptions from the visual, vestibular and proprioceptive systems (Drummond, 2002). Experimental MS is commonly induced in virtual reality environments (Lin et al., 2002) or by a rotating drum, with or without optokinetic stimulation (Drummond, 2002; Wan and Hu, 2003). However, it is unclear whether virtual-reality-induced or rotating-drum-induced MS involve the same underlying neural mechanisms as that induced by daily life experiences, such as sitting in a moving vehicle (Golding, 2006).

Most of the previous studies examined the relationship between the MS levels and the autonomic nervous system by comparing the HRV indices before and during experimental motion exposure over a period of time (e.g., Uijtdehaage et al., 1993). Therefore, the short-term or temporal pattern of the autonomic control of the HRV indices may obscure important information (Morrow et al., 2000). Only two studies correlated MS symptoms with temporal changes in the HRV indices (Gianaros et al., 2003; Ohyama et al., 2007), and the results remained inconclusive. The reasons for the uncertain relationship between the MS levels and the HRV indices may relate to the large inter- and intra-subject variability of self-reported MS, which was assessed subjectively and intermittently (Beckers et al., 2006; Bos and Bles, 1998; Ohyama et al., 2007; Peng et al., 2007). For example, MS symptoms were verbally reported at 1-min intervals (Holmes and Griffin, 2001; Young et al., 2003; Ziavra et al., 2003). This type of intervention can unexpectedly provide opportunities for subjects to temporarily alleviate their MS symptoms to an undetermined extent and adversely influence the interrelationship between MS and the HRV indices (Sang et al., 2003). Therefore, to accurately correlate the HRV indices with MS severity, studies using high-temporal resolution and minimal measurement interventions are required.

Sympathovagal activities can be modulated by respiration. For example, a slow breathing technique can enhance autonomic function by decreasing sympathetic activity and increasing parasympathetic activity (Jerath et al., 2006; Pinheiro et al., 2007). The HF component is known as respiratory sinus arrhythmia (Graham et al., 2009; Grossman and Taylor, 2007) and is synchronous with respiratory patterns (Montano et al., 2009). Irregular respiration could change sympathovagal activities or its balances, which are reflected in the HRV indices (Roach et al., 2004; Jerath et al., 2006; Grossman and Taylor, 2007; Pinheiro et al., 2007; Graham et al., 2009). Sang et al. (2003) also reported that controlling breathing might be effective for controlling nausea. In addition to controlling the breathing by the subjects, the respiration rhythm and depth can be altered by other behaviors. For instance, swallowing can inhibit respiration because of the respiratory and swallowing coordination mechanisms (Paydarfar et al., 1995; Cichero, 2006). Similarly, during retching, pulmonary ventilation suppresses to protect the airway from gastric acid (Cichero, 2006). However, it remains unclear in the literature whether and how the above and other self-adjustments adopted by the subjects to cope with the MS-induced illness could vary the relationships between the MS severity and HRV indices. This study aims to investigate whether and to what extent the self-adjustments can affect the MS–HRV relationship.

Video recordings seem a good source for assessing subjects' behaviors. Particularly, three behaviors, deep breathing, swallowing and the retching, could be reliably identified from the videos. The specific goal of this study is then to assess the influences of the self-adjustments, measured by the three behaviors, on the MS–HRV relationship.

This study first correlates the HRV indices with MS severity and then investigates whether the self-adjustments influence the relationship between MS levels and HRV indices. The experiments were conducted using a motion driving simulator comprising a virtual reality-based tunnel driving paradigm and a real vehicle mounted on a motion platform with 6 degrees of freedom (Lin et al., 2005). The influence of behavioral responses on the temporal relationship between the MS levels and HRV indices was assessed and modeled by simple linear regression.

2. Methods

2.1. Subjects

In total, 26 volunteers (11 females and 15 males; mean age 25 ± 3 years) with normal or corrected-to-normal vision were paid to participate in this MS experiment. All of the subjects were healthy and had no history of gastrointestinal, cardiovascular, neurological or psychological disorders. For accurate evaluation of the HRV indices, the subjects were required to not imbibe alcoholic or caffeinated drinks or to participate in strenuous exercise 1 day prior to the experiments. The experiments were performed in the morning (09:00–12:00) or afternoon (14:00–17:00). The subjects were required to fast for 2 hours prior to the experiments. The experimental protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan. The subjects were informed of the experimental procedure, and written consent was obtained from each subject prior to the experiment.

Two exclusion criteria were used in this study. First, the subjects were required to complete the entire experiment (65 min, including the baseline, MS-induction, and recovery session). Second, the subjects were required to report their MS levels continuously during the whole experiment. Two of the 26 subjects felt very uncomfortable and vomited (severe MS) during their experiments and they failed to finish the entire experiment. Four of the 26 subjects failed to report their MS levels because they fell asleep during the experiments. Thus, the data from those six subjects were excluded from the subsequent data analysis.

2.2. Experimental setup

The experiments were performed in a dynamic virtual reality environment comprising a 360° virtual reality scene (Fig. 1A) and a motion platform with 6 degrees of freedom (Fig. 1B) (Lin et al., 2005). The virtual reality-based tunnel-driving paradigm simulated a car being driven in a long and winding tunnel at a fixed speed of 100 km/h. The virtual reality scene was projected by seven projectors (BARCO, Belgium), each of which was controlled by a personal computer and synchronized via a local area network. The refresh rate of the virtual reality scene was 60 Hz. A real vehicle (Fig. 1B), with its engine and other unnecessary parts removed, was mounted on the motion platform at the center of the virtual reality room. This type of dynamic virtual reality environment provided a combination of visual, vestibular and proprioceptive sensations simultaneously.

Prior to the data collection, all of the subjects were required to view the virtual reality scene for > 10 min until they had fully adapted to the virtual reality environment. During each experiment, the subject sat alone and passively viewed the driving scenery as a passenger in the simulator. Each MS experiment included three consecutive sessions without interruption (Fig. 1D): 10 min of straight road as a baseline (baseline session); 40 min of a long, winding road for inducing MS (MS-induction session); and, finally, 15 min of straight road for recovery (recovery session).

2.3. Data acquisition

2.3.1. Behavioral data

2.3.1.1. MS level. During the MS experiment, subjects continuously reported their MS levels using a sliding switch, which was appended to

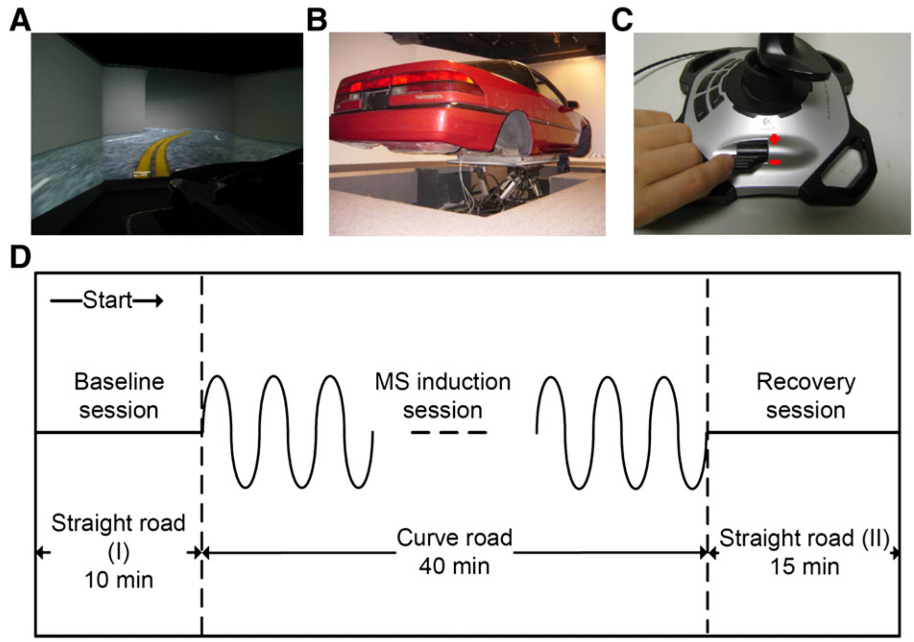

Fig. 1. The dynamic-motion driving environment and a schematic diagram of an MS experimental paradigm. (A) This photograph shows the surrounding tunnel scenes. (B) This photograph shows a motion platform with 6 degrees of freedom with a car body mounted on a support. (C) The subjects report their MS levels by tuning the slide-type switch, which is located in the red circle of the joystick, throughout the entire experiment. (D) The experiment comprises 3 sessions: in the first session (baseline session), the subject rode for 10 min on a straight virtual-reality road; in the second session (MS-induction session), the subject rode for 40 min on a virtual-reality winding road; and, in the third session (recovery session), the subject rode for 15 min on a virtual-reality straight road.

a commercially available joystick (PN 963290-0121, Logitech, Swiss), as shown in Fig. 1C. The subjects were required to report their MS levels immediately by changing the switch position when their sickness level changed; the top position of the switch represented severe retching. For instance, when the subjects started to feel sick after the onset of MS induction, they could slide the switch from zero to a higher position. The position of the sliding switch could thus continuously reflect the severity of the MS. The switch positions were digitized at a 60-Hz sampling rate with a 16-bit vertical resolution (0–65,535) using emulation software (WorldToolKit, WTK, library and Visual C++ version 6.0, Microsoft, USA), and the digitized MS levels were delivered to and stored in a laptop (ASUS M24C3) via a universal serial bus (USB) interface for offline analysis. When the experiment began, the emulation software started sending trigger signals to the signal acquisition system to synchronize electrocardiogram (ECG) signals with the digitized MS levels.

After finishing the entire experiments, the subjects were required to complete a MS questionnaire (modified from Holmes and Griffin, 2001; Yokota et al., 2005) on which they indicated their maximum MS level during the experiment and reported what type of self-adjustments they used when they felt uncomfortable. In the questionnaire, the subjects used 6 levels (0–5) to report their MS symptoms (0 = no MS, 1 = stomach awareness, 2 = stomach discomfort, 3 = slight retching, 4 = moderate retching, and 5 = severe retching). The subjective reports (MS questionnaire) were used to rescale each individual subjects' digitized MS levels.

2.3.1.2. Video monitoring. A video camera (MT-772S CCD Camera) was installed in the vehicle to monitor each subject's behavioral responses. The video frame rate was 30 frames per second, and the number of effective pixels of the video image was 512×492 (H×V). The video images were digitized and stored in a laptop (ASUS M24C3) via a USB interface for offline analysis.

2.3.2. ECG data

ECG signals were acquired by two electrodes in a modified leads II configuration (Griffiths et al., 2007). The positive and negative leads were placed on the left arcus costalis and right clavicle, respectively. The ECG signals were amplified (NuAmps, Compumedics Ltd., VIC, Australia) and recorded at a 500-Hz sampling rate and notch-filtered at 60 Hz. The ECG signals and MS severity were synchronized using trigger signals generated by the emulation software as mentioned above.

2.4. Data analysis

2.4.1. Analysis of MS level

The digitized MS levels were rescaled into 6 levels (0–5) according to each subject's MS questionnaire. First, the digitized MS levels (0–65,535) were divided by the individual subject's maximum value and then multiplied by the individual subject's maximum MS value that was reported in the MS questionnaire (0–5). These rescaled MS levels were smoothed using the moving average method with a 5-min moving average window overlapped by 4.5 min (the same process as used in analyzing the HRV indices).

2.4.2. Analysis of video behavior

The recorded video images of each subject were used to identify whether the subjects performed self-adjustments to relieve the discomfort of the MS. Three types of behavioral responses, including deep breathing, swallowing and retching, were identified and counted as self-adjustments during the experiment from the recorded video images. Deep breathing was defined as movements that elevated the clavicle and shoulders in subjects who had long inspiration and expiration responses. Swallowing was identified by the changes in the jaw and throat positions. Retching was defined by the subject opening and/or covering his/her mouth with his/her hands while the throat moved vertically and the subject dry heaved. To evaluate the variations across raters, three raters independently counted a single subject's numbers of deep breathing, swallowing and retching based on the definitions of these three self-adjustments in the subjects' videos. The Krippendorff's alpha was used to test the variations and consistency across 3 raters. The Krippendorff's alpha was estimated using MATLAB (The Mathworks, Inc.) and the open source code (Jana

Eggink; http://www.mathworks.com/matlabcentral/fileexchange/36016-krippendorffs-alpha). This open source code has been verified against an existing SPSS macro (The SPSS, Inc.). Table 1 shows the rating results of the three raters. The ratings were remarkably consistent across 3 independent raters with the inter-rater reliability alpha of 0.9093 (Krippendorff's alpha), suggesting that the self-adjustments can be accurately identified and counted from the subjects' videos according to the definitions of these behaviors.

2.4.3. Analysis of ECG data

The HRV was analyzed according to the modified procedures developed by Kuo and Yang (2002) (Fig. 2). Briefly, the QRS peaks were first identified in the digital ECG signals using spike-detection algorithms (Fig. 2A) (Kuo and Chan, 1992). A QRS rejection procedure was then utilized to remove irregular QRS complexes resulting from noise or unrelated behavioral responses. For each heartbeat, the QRS rejection procedure evaluated the amplitude of the Q–R wave (AQR), amplitude of the R–S wave (ARS), duration of the Q–S wave (TQS), and duration of the R–S wave (TRS). Each heartbeat was then scored based on the values of these 4 indices (AQR, QRS, TQS and TRS). If an index of a heartbeat fell within the range of its mean ± 4 standard deviation, this heartbeat was assigned 1 point. Hence, these 4 indices were summed as a final score in a range of 0–4 for each heartbeat. A heartbeat with a final score < 3 was discarded as noise.

The temporal position of the R peak for each valid QRS complex, which was screened by the above-mentioned procedures, was defined as a heartbeat. The interval between two successive R peaks (R–R interval) was calculated from the time series of the R peaks. The R–R intervals were outside of either the 0.5- to 1.3-S range (regular R–R interval range; Roach et al., 2004) or the range defined by the mean ± 3 standard deviation were eliminated from further analysis. The validated R-R values were subsequently resampled and interpolated at a 250-Hz sampling rate to generate continuity in the time domain. The R–R intervals of the entire experiment were subjected to a fast Fourier transform with a 5-min Hamming window overlapped by 4.5 min (Fig. 2B). This study focused on three frequency bands: the VLF (0.003–0.04 Hz), LF (0.04–0.15 Hz), and HF (0.15–0.4 Hz) bands (Fig. 2C; Kuo and Yang, 2002). The powers of the LF and HF bands were normalized by the total power minus the power of the VLF band, and the components were represented in normalized units (NLF and NHF); that is, NLF = LF/(total power − VLF) ∗ 100% and NHF = HF/(total power − VLF) × 100%, where total power = LF + HF + VLF. Camm et al. (1996) showed that normalized LF and HF could minimize the effects of changes in the total power on the values of the LF and HF; the normalized LF and HF also could separate out the influence of the sympathetic and parasympathetic nervous systems on the sympathovagal balance (Madden et al., 2008). The sympathovagal balance was calculated as the ratio of the LF power to the HF power (LF/HF ratio). The natural logarithmic transformation was applied to the LF/HF ratio, that is, LF/HF ratio = log (LF/HF). The time series of the NLF, NHF, and LF/HF ratio were then smoothed by the moving average method (Matlab Curve Fitting Toolbox, function “smooth” with a moving setting of 25; Fig. 2E).

Table 1
Summary of the statistics of a single subject's numbers of deep breathing, swallowing and retching independently counted by three raters for assessing inter-rater variability.

Rater (n = 3)	Deep breathing	Swallowing	Retching	Total number of self-adjustments
1	27	13	5	45
2	18	18	5	41
3	21	13	8	42
Mean ± STD	22 ± 5	15 ± 3	6 ± 2	43 ± 2

2.5. Spearman's rank correlation coefficient

Spearman's rank correlation coefficient was used to assess the relationship between the changes in the individual HRV indices (the continuous NLF, NHF, and the LF/HF ratio) and the subjective MS levels. Because the NLF and NHF values were normalized by the total power minus the power of the VLF, the sum of the NLF and NHF values was 100%. Therefore, the temporal changes of the NLF and NHF were opposite, and the changes in LF/HF ratio during the experiment were similar to the changes of the NLF. The similarities in the changes were also revealed in the Spearman's rank correlation coefficients between the MS levels and the HRV indices.

The subjects were classified into three groups according to their Spearman's rank correlation coefficients between the MS levels and the changes in the NLF. The subjects who had coefficients greater than 0.5 were classified into Group I, and the subjects who had coefficients from 0 to 0.5 were classified into Group II. The subjects in Group III were those had negative correlations between the MS levels and the NLF.

2.6. Changes in the HRV indices for different MS levels across different groups

To assess the changes in the HRV indices (NHF, NLF and LF/HF ratio) for different MS levels across the three groups (I–III), the HRV indices were analyzed and compared according to the following procedures. The HRV indices of three groups were processed separately with the following sub-steps. First, the HRV indices of the individual subjects in each group were sorted by his/her MS levels from 0 to 5. Second, each of the sorted HRV indices was normalized by the *z*-score normalization method:

$$z = (x - u)/\sigma \tag{1}$$

where x is a raw HRV index to be standardized and u and σ are the mean and standard deviation of the HRV index, respectively, which their corresponding MS levels <= 1. Third, to assess and compare the various changes of the HRV indices for different MS levels among the three groups, the normalized HRV indices of each subject within each group were selected and classified into three periods by the MS rating; these were the low-MS (MS levels <= 1), the medium-MS (2 <= MS levels < 3) and the high-MS (4 <= MS levels < 5) periods. The changes in the HRV indices within each group for the three different MS periods and the effects of inter-subject variation on the changes in the HRV indices across the three different groups were compared statistically by the Kruskal–Wallis test and the Bonferroni correction.

2.7. Simple linear regression

A simple linear regression was used to evaluate the relationship across subjects between the number of self-adjustments and the Spearman's rank correlation coefficients, which assessed the relationship between the changes of the individual HRV indices (the continuous NLF, NHF and LF/HF ratio) and the subjective MS levels; a linear regression was performed to determine the effects of the self-adjustments maneuvers on the relationship between the MS levels and HRV indices. A simple linear regression fits a straight line though n points and makes the sum of the squared residuals of the model as small as possible (Neter et al., 1996). The simple linear regression model can be described by the following equation:

$$Y = a + bX \tag{2}$$

where Y and X consisted of n data points $\{Y_i, X_i\}$. Y_i was the response variable (e.g., the number of self-adjustments), X_i was the input variable (e.g., Spearman's rank correlation coefficient between the MS levels

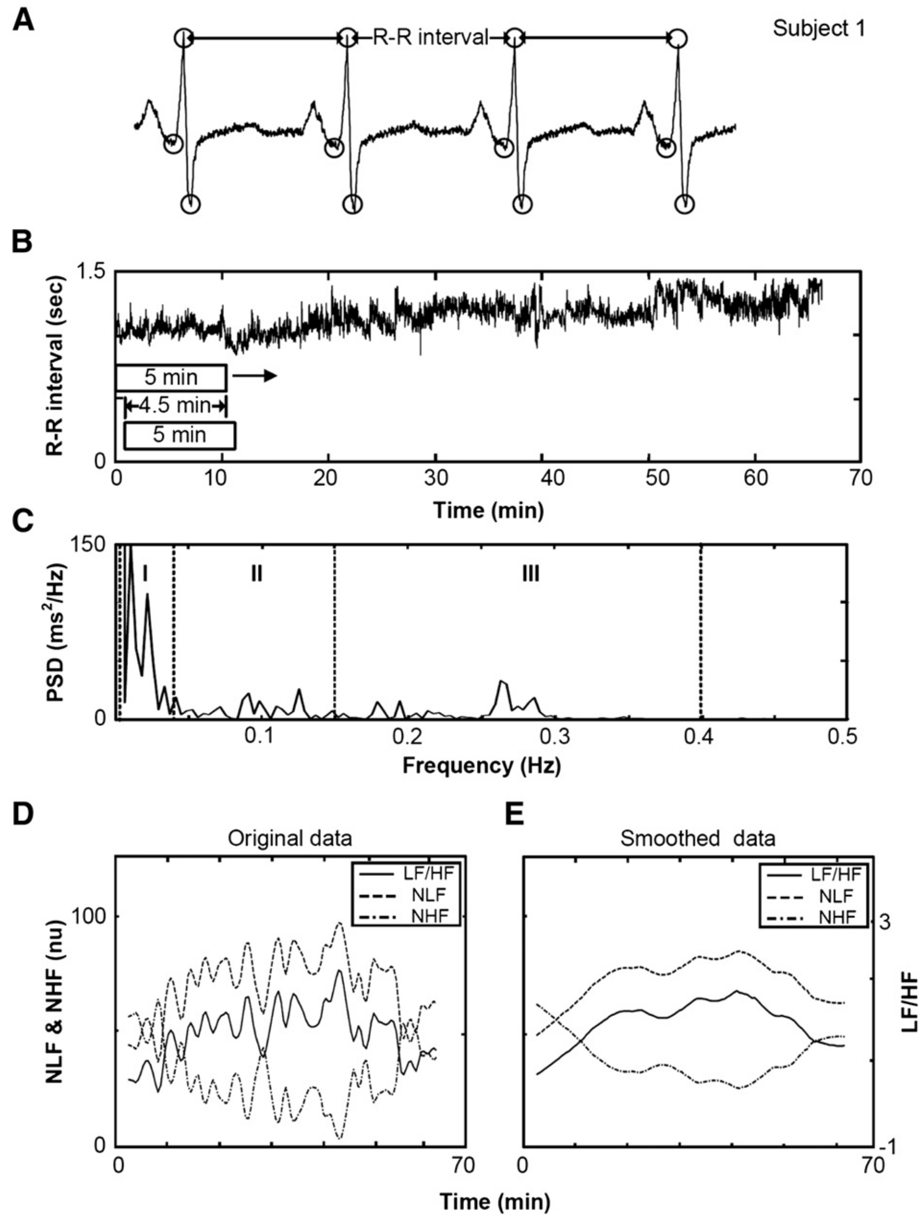

Fig. 2. A schematic representation of the method used for spectral analysis of the HRV for 1 subject. (A) The surface electrocardiogram. (B) A Matlab program is used to detect QRS peaks, compute individual R–R intervals and save the results as a tachogram. (C) Three major components, very low frequency (VLF, I), low frequency (LF, II) and high frequency (HF, III), are derived from the power spectrum density of the R–R intervals. (D) The tachogram is subjected to a fast Fourier transform with a 5-min Hamming window overlapped by 4.5 min to obtain the time series of the HRV indices. (E) The time series of the HRV indices are then smoothed using the Matlab function "smooth" (Matlab Curve Fitting Toolbox).

and the HRV indices), and i represented the number of each subject. The regression coefficients a and b were determined using the Matlab function "regress" (Matlab statistics Toolbox), which minimized the sum of the squared residuals of the model.

2.8. Statistical analyses

The differential effects of the MS levels on the changes in the HRV indices within each group, the inter-subject variation in the changes in the HRV indices across the three different groups and the frequency of self-adjustment among the three groups were also assessed by the Kruskal–Wallis test and the Bonferroni correction. The significance level was set as $p<0.05$.

3. Results

3.1. Motion sickness (MS) levels and heart rate variability (HRV) indices over time

Fig. 3A shows the time course of the MS levels of a sample experiment from a representative subject (subject 1). A biphasic change in the MS levels was induced by the dynamic virtual reality-based tunnel scenes. The MS level of subject 1 remained at 0 during the initial 10 min of the straight driving task. After the subject entered the winding-road session, the MS level then increased steadily after 1 min and peaked at 29 min. The MS level dropped prior to the end of the winding-road driving task and returned to 0 during the recovery session.

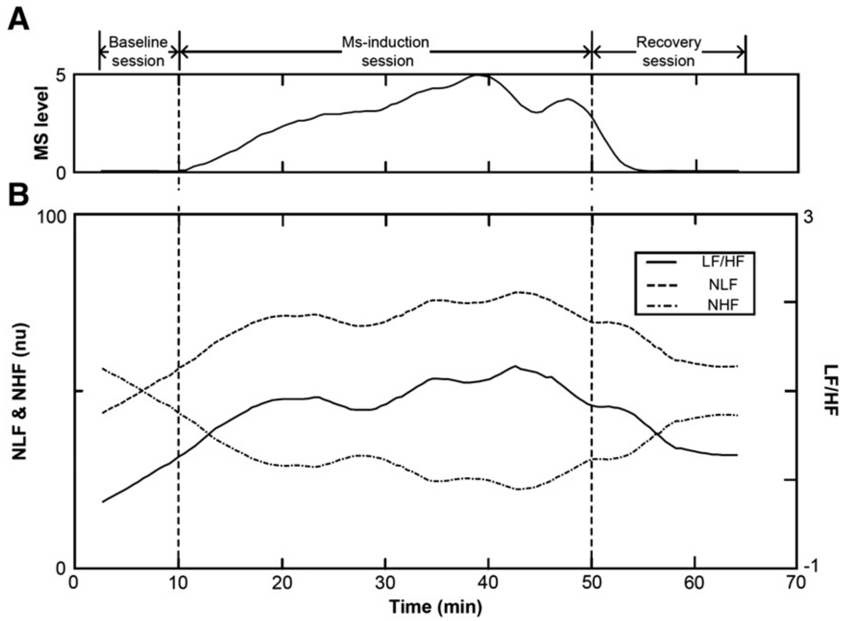

Fig. 3. Changes in the MS levels and the HRV indices during the driving experiment. (A) The time course of the self-reported MS for a typical subject (subject 1). (B) The smoothed NLF (dashed line), NHF (dash-dotted line) and the LF/HF ratio (solid line) of the subject during the driving experiment.

The onset of MS increase varied across subjects ($n=20$). Approximately 20% ($n=4$) of the subjects started experiencing MS symptoms within 1 min after the winding-road session began, whereas 40% of the subjects ($n=8$) did not feel sick until 5–8 min after entering the winding-road session. The remaining 8 subjects (40%) reported MS as early as at the end of the baseline session. On average, the occurrence of the maximal MS level was at approximately 44 ± 6 min. Furthermore, the absolute values of the peak MS level varied among subjects. Twelve subjects (60%) ranked their maximal MS levels as 5, 2 subjects (10%) ranked their maximum MS level as 4–5, 3 subjects (15%) ranked their maximum MS level as 3–4, and 3 subjects (15%) ranked their maximum MS level as 1.5–2.5.

Although the exact temporal profile of the MS levels varied among the subjects, the group trend of the MS levels resembled the pattern of subject 1 (Fig. 3A). These experimental results demonstrated that a dynamic virtual reality environment can induce MS. Moreover, MS severity increased progressively after the virtual-reality scenes began simulating a winding road. However, most subjects' (60%, $n=12$) MS levels did not return to the baseline level after the virtual-reality session returned to the straight-road session, suggesting a residual effect.

Fig. 3B shows the changes in the HRV indices (the smoothed NLF, NHF and the LF/HF ratio) over the entire experiment from the representative subject (subject 1). The NLF and LF/HF ratio increased progressively as the experiment proceeded to the MS-induction session, whereas the NHF generally decreased. During the recovery session, the NLF and LF/HF ratio decreased, whereas the NHF increased as the MS level gradually returned to the baseline level.

3.2. The temporal relationship between the MS levels and the HRV indices

Fig. 4 shows the sorted correlation coefficients between the MS levels and the NLF, NHF and LF/HF ratios for the 20 subjects. The correlation coefficients between the MS levels and the HRV indices varied across subjects. Thirteen subjects (65%) had MS levels that were positively correlated with the NLF and the LF/HF ratio and negatively correlated with NHF. Of the 13 subjects, seven (35%, Group I) had correlation coefficients greater than 0.5 (NLF and LF/HF) or smaller than -0.5 (NHF), and the rest six (30% of subjects, Group II) had correlation coefficients in the range from 0 to 0.5 (NLF and LF/HF) or from 0 to -0.5 (NHF). For the remaining seven of the twenty subjects (35%, Group III), the MS levels negatively correlated with the NLF and the LF/HF ratio and positive correlated with the NHF.

3.3. Differential effects of the MS levels on the HRV indices in the three groups

Fig. 5 compares the changes in the HRV indices across the three groups (I, II and III) during the low-, medium- and high-MS periods. The results of the three groups all showed that the distributions of the HRV indices during the low-, medium- and high-MS periods were significantly different (Table 2; by the Kruskal–Wallis test). Based on the difference between the low- and medium-MS periods as well as the difference between the low- and high-MS periods, the subjects in Groups I and II had statistically significant increases in the NLF and LF/HF ratio and significant decreases in the NHF (NLF, $p<0.001$; the LF/HF ratio, $p<0.001$; NHF, $p<0.001$; by the Bonferroni correction; Fig. 5A and B). For subjects in Group I (35%, $n=7$), the NLF and the LF/HF ratio increased significantly, and the NHF decreased significantly during the high-MS period compared with the HRV indices during the medium-MS period (Fig. 5A; by the Bonferroni correction). For the subjects in Group II (30%, $n=6$), although their NLF and LF/HF ratio increased and their NHF decreased during the high-MS period in comparison with those during the medium-MS period, the differences were not statistically significant (Fig. 5B; by the Bonferroni correction). The subjects in Group III (35%, $n=7$) had opposite HRV responses during the medium- and high-MS periods compared with the subjects in Group I (35%, $n=7$). Specifically, for the subjects in Group III, the NLF and the LF/HF ratio decreased progressively as the MS levels increased, whereas the NHF generally increased (Fig. 5C).

Fig. 6 shows the differences in the changes in the HRV indices during the low-, medium- and high-MS periods across the three groups. No differences were found in the distribution of the HRV indices during the low-MS period among the three groups. The HRV indices during the medium- and high-MS periods varied significantly among the three groups (Table 3). Based on the difference between the low- and medium-MS periods, the subjects in Group I had larger fluctuations in the HRV indices compared with the subjects in Group II. That is, the increases in the NLF and the LF/HF ratio and decreases in the NHF of Group

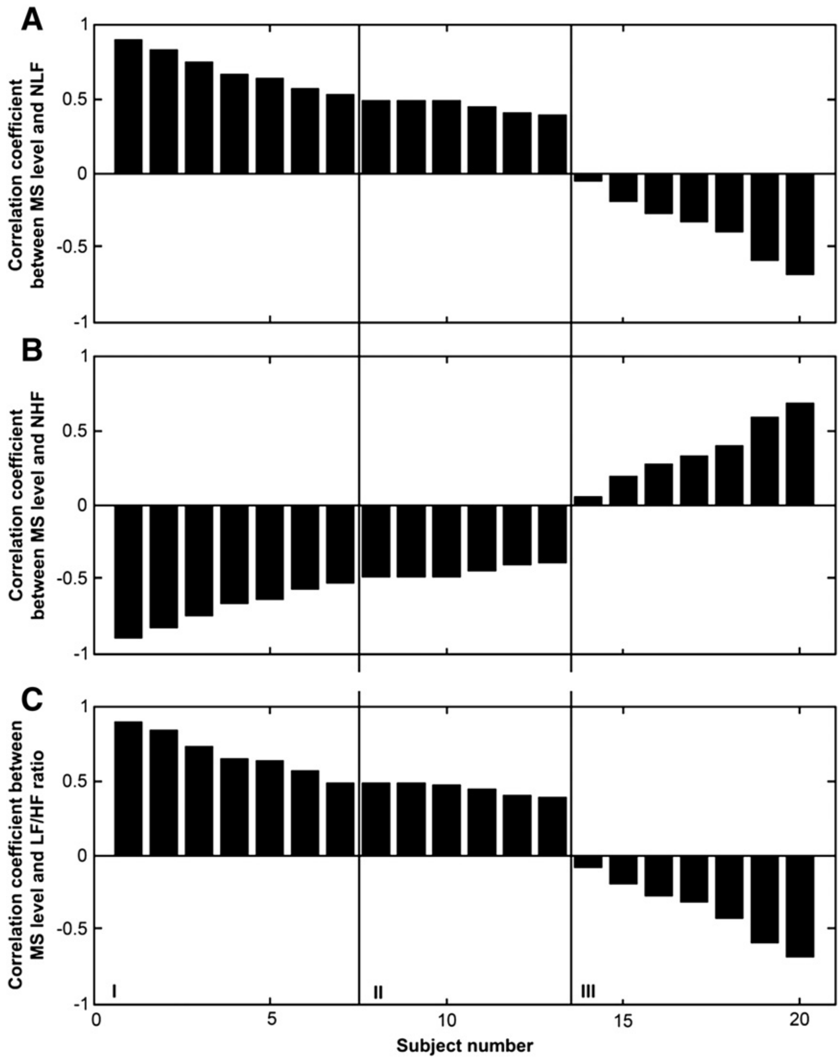

Fig. 4. Variations in the correlation coefficients between the MS levels and NLF (A), NHF (B) and the LF/HF ratio (C) across all of the subjects. The 20 subjects were divided into 3 groups (I, II and III) according to the correlation coefficients between their MS levels and NLF values.

I subjects were significantly larger than those of the Group II subjects during the medium-MS period ($p<0.01$; by the Bonferroni correction). Similar changes in the HRV indices between Groups I and II were found during the high-MS period. The subjects in Group III showed an opposite change in the HRV indices between the low- and medium-MS periods as well as the low- and high-MS periods. Unlike the subjects in Groups I and II, the subjects in Group III had decreases in the NLF and the LF/HF ratio and increases in the NHF values during the medium- and high-MS periods.

3.4. Effects of the self-adjustments on the MS -HRV relationship

The number of self-adjustments was assessed based on the videos and completely independent of the HRV analysis. The differences in the number of self-adjustments among the three groups were not statistically significant ($p=0.52$; by the Kruskal–Wallis test). Fig. 7 shows the effects of the self-adjustments on the correlation coefficients between the MS levels and the HRV indices. The correlation coefficients between the MS and NLF relationship decreased monotonically with increasing numbers of self-adjustments (Fig. 7A). Similar effects from the self-adjustments were also revealed on the variations in the correlation coefficients between the MS levels and the LF/HF ratio (Fig. 7C). Moreover, the correlation coefficients of the MS–NHF relationship increased linearly with an increasing number of self-adjustments (Fig. 7B). A linear relationship was evident between the number of self-adjustments (y) and the correlation coefficients between the MS levels and the HRV indices (linear regression: $y=57.65–13.19\times NLF$; $y=57.65+13.19\times NHF$; $y=57.61–13.24\times LF/HF$ ratio; R^2 statistic $=0.44$ and $p<0.005$). These results indicated that the sympathetic activities were reduced whereas the parasympathetic activities were increased with larger numbers of self-adjustments during the MS induction.

4. Discussion

4.1. Correlations between the MS levels and the HRV indices

The present study demonstrates that the HRV indices derived from recorded ECG signals during the low-MS period were significantly different from those during the medium- and high-MS periods. Thus, the experimental results suggest that autonomic control is involved in the development of MS symptoms. Approximately 65% of the subjects ($n=13$) had positive correlations of the MS levels with the NLF and with the LF/HF ratio and negative correlations between the MS levels and the NHF; the correlations were analyzed by Spearman's rank correlation coefficient. More than half of the subjects had correlation coefficients above 0.5. This result is consistent with previous studies showing that exposure to motion sickness stimulation increases cardiac sympathetic activity and decreases cardiac

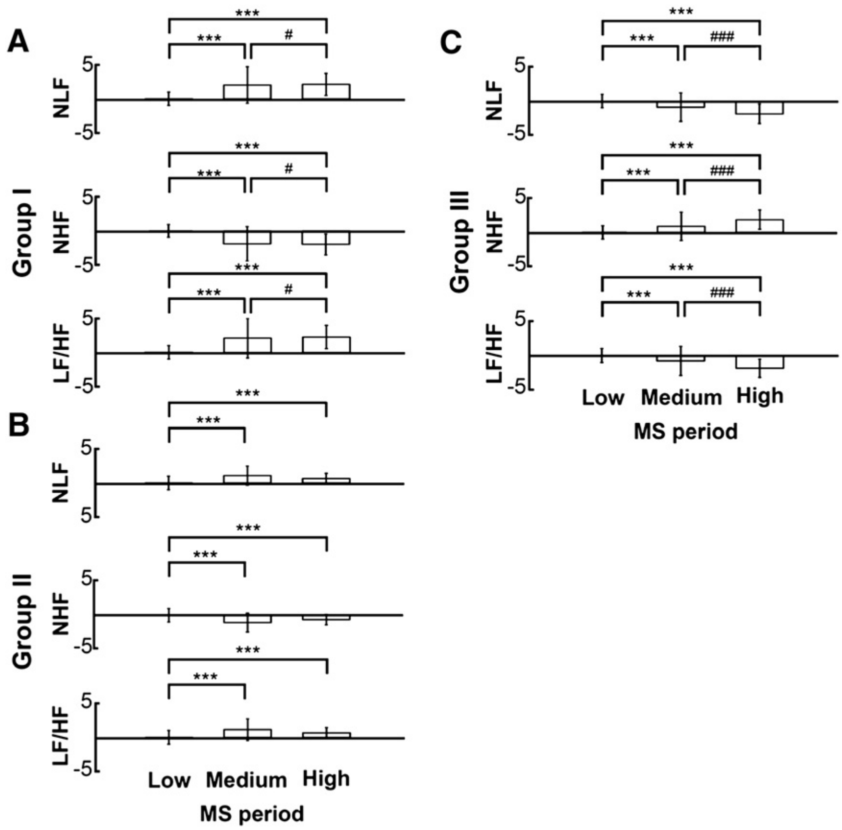

Fig. 5. Differential effects of the MS levels on the HRV indices in Group I (A), Group II (B) and Group III (C). The results are represented as the mean ± standard deviation, and the statistical analysis results are noted as follows: * $p<0.05$; ** $p<0.01$; *** and ### $p<0.001$.

parasympathetic activity, as reflected in the HRV (Holmes and Griffin, 2001; Yokota et al., 2005). However, Ohyama et al. (2007) reported that during exposure to a virtual-reality environment, MS-induction increased sympathetic activity without vagal changes. The discrepancy between the Ohyama's group's results and our results might be attributed to difference in the methods used to assess the MS levels and the autonomic functions. The normalized HRV indices have been proven to best reflect the sympathetic and parasympathetic responses (Arlt et al., 2003; Chen et al., 2006). Furthermore, the sliding switch used by our subjects to continuously rate their MS levels could have also contributed to the differences. The advantage of using the sliding switch for continuous MS reporting was that the subjects were not interrupted during the continuous experiment sessions. If the subject's MS level was determined every minute by interrupting the experiment, the subject most likely could receive momentarily relief from the MS symptoms. In turn, the MS levels could be different due to the continuous uninterrupted MS. As a result, the MS induced in the present study would more closely resemble our real-world experiences. Although we cannot completely rule out the possibility that our method might interfere with the subject's MS experience. The interference in our method should be minimal compared with the methods used in previous studies (Holmes and Griffin, 2001; Young et al., 2003; Ziavra et al., 2003).

In this study, approximately 35% of the subjects ($n=7$) showed the negative correlations between the MS levels and the NLF as well as the LF/HF ratios. These subjects had higher NHF values during the medium- and high-MS periods in comparison with the NHF values of the subjects with positive MS–NLF and MS–LF/HF ratio relationships. In addition, these subjects reported that they felt sickness immediately after the onset of the experiment and constantly adjusted themselves to relieve the sick feeling. Studies have suggested that subjects could easily suffer from cybernetic sickness caused by an initial exposure to a virtual-reality scene (Morrow et al., 2002). Although our subjects were required to adapt to the virtual-reality scene for 10 min before the MS experiment to prevent cybernetic sickness, the results revealed that the 10-min practice time might not be sufficient for some subjects (e.g., Group III subjects). The duration for adapting to the virtual-reality

Table 2
Summary of the statistics for the effects of MS levels on the changes in the HRV indices in the three groups.

Group	HRV indices	MS period			Degrees of freedom	F-statistic	*p*-value
		Low	Medium	High			
Group I	NLF	0.0 ± 1.0	2.0 ± 2.7	2.1 ± 1.6	F(2,585)	254.68	$p<0.001$
	NHF	0.0 ± 1.0	− 2.0 ± 2.7	−2.1 ± 1.6	F(2,585)	254.68	$p<0.001$
	LF/HF	0.0 ± 1.0	2.1 ± 3.0	2.2 ± 1.7	F(2,585)	250.23	$p<0.001$
Group II	NLF	0.0 ± 1.0	1.1 ± 1.4	0.6 ± 0.8	F(2,483)	57.49	$p<0.001$
	NHF	0.0 ± 1.0	− 1.1 ± 1.4	−0.6 ± 0.8	F(2, 483)	57.49	$p<0.001$
	LF/HF	0.0 ± 1.0	1.1 ± 1.6	0.6 ± 0.8	F(2, 483)	52.77	$p<0.001$
Group III	NLF	0.0 ± 1.0	− 0.9 ± 2.1	− 1.9 ± 1.4	F(2,541)	99.9	$p<0.001$
	NHF	0.0 ± 1.0	0.9 ± 2.1	1.9 ± 1.4	F(2, 541)	99.9	$p<0.001$
	LF/HF	0.0 ± 1.0	− 0.8 ± 2.1	− 1.8 ± 1.3	F(2, 541)	100.25	$p<0.001$

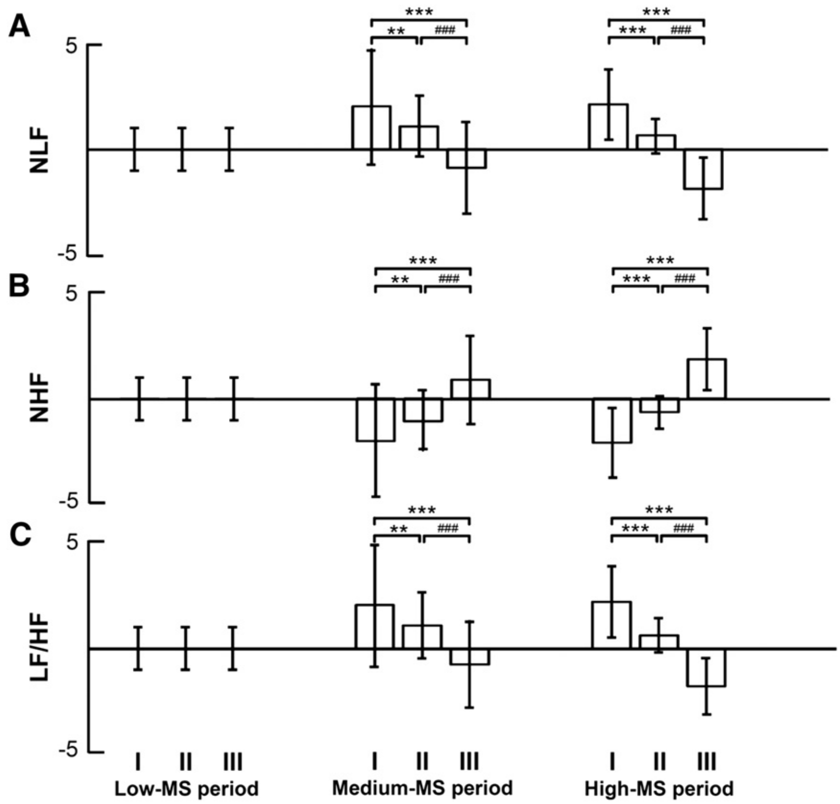

Fig. 6. The group differences for changes in the NLF (A), NHF (B) and LF/HF (C) during the low-, medium- and high-MS periods. The baseline in all of the figures is the low-MS period (mean ± standard deviation; ** $p<0.01$; *** and ### $p<0.001$; by the Bonferroni correction). Note the decreased or reversed changes in the HRV indices in Groups II and III during the medium- and high-MS periods.

scene will be more appropriately determined on an individual basis in future studies.

4.2. Effects of self-adjustments on the relationship between the MS levels and the HRV indices

Several studies reported that no correlation exists between self-reported MS symptoms and changes in the HRV indices (Beckers et al., 2006; Bos and Bles, 1998; Ohyama et al., 2007; Peng et al., 2007). They suggested that this result may be caused by large inter- and intra-subject variations. Two studies reported that self-adjustments could affect the relationship between MS and sympathovagal activities, which were measured with the HRV indices when the conscious subjects actively adjusted themselves to relieve the discomfort of MS during the experiments (Jerath et al., 2006; Pinheiro et al., 2007). Hence, we hypothesized that the large inter-subject variation might be partially caused by the subjects' self-adjustments, which were used to ease the illness induced by the MS. According to the MS questionnaire collected at the end of experiments, the subjects reported that they performed some self-adjustment to reduce their discomfort when they felt sick. This study identified three types of self-adjustments, deep breathing, swallowing and retching, from the videos; these self-adjustments occurred frequently when the subjects felt sick. Even though the subjects adopted the self-adjustments to reduce MS symptoms, this study cannot prove whether more self-adjustments would lead to lower MS as the subjects might start adjusting themselves after they felt MS. It is thus difficult to assess the effects of self-adjustments on the MS itself in this study. Results of the simple linear regression however clearly indicated that the relationship between the MS severity and the HRV indices was sensitive to the three self-adjustments (deep breathing, swallowing and retching) during the MS experiment. A linear relationship was evident between the number of self-adjustments and the MS–HRV correlation coefficients. For instance, the correlation coefficients of the MS–NLF relationship dropped from a positive to a negative value as the number of

Table 3
Summary of the statistics for the effects of group differences on the changes in the HRV indices during the low-, medium-, and high-MS periods.

MS period	HRV indices	Group			Degrees of freedom	F-statistic	*p*-value
		I	II	III			
Low	NLF	0.0 ± 1.0	0.0 ± 1.0	0.0 ± 1.0	F(2,922)	0.25	$p=0.88$
	NHF	0.0 ± 1.0	0.0 ± 1.0	0.0 ± 1.0	F(2,922)	0.25	$p=0.88$
	LF/HF	0.0 ± 1.0	0.0 ± 1.0	0.0 ± 1.0	F(2,922)	0.19	$p=0.91$
Medium	NLF	2.0 ± 2.7	1.1 ± 1.4	−0.9 ± 2.1	F(2,372)	95.46	$p<0.001$
	NHF	−2.0 ± 2.7	−1.1 ± 1.4	0.9 ± 2.1	F(2,372)	95.46	$p<0.001$
	LF/HF	2.1 ± 3.0	1.1 ± 1.6	−0.8 ± 2.1	F(2,372)	83.3	$p<0.001$
High	NLF	2.1 ± 1.6	0.6 ± 0.8	−1.9 ± 1.4	F(2,315)	234.64	$p<0.001$
	NHF	−2.1 ± 1.6	−0.6 ± 0.8	1.9 ± 1.4	F(2,315)	234.64	$p<0.001$
	LF/HF	2.2 ± 1.7	0.6 ± 0.8	−1.8 ± 1.3	F(2,315)	239.47	$p<0.001$

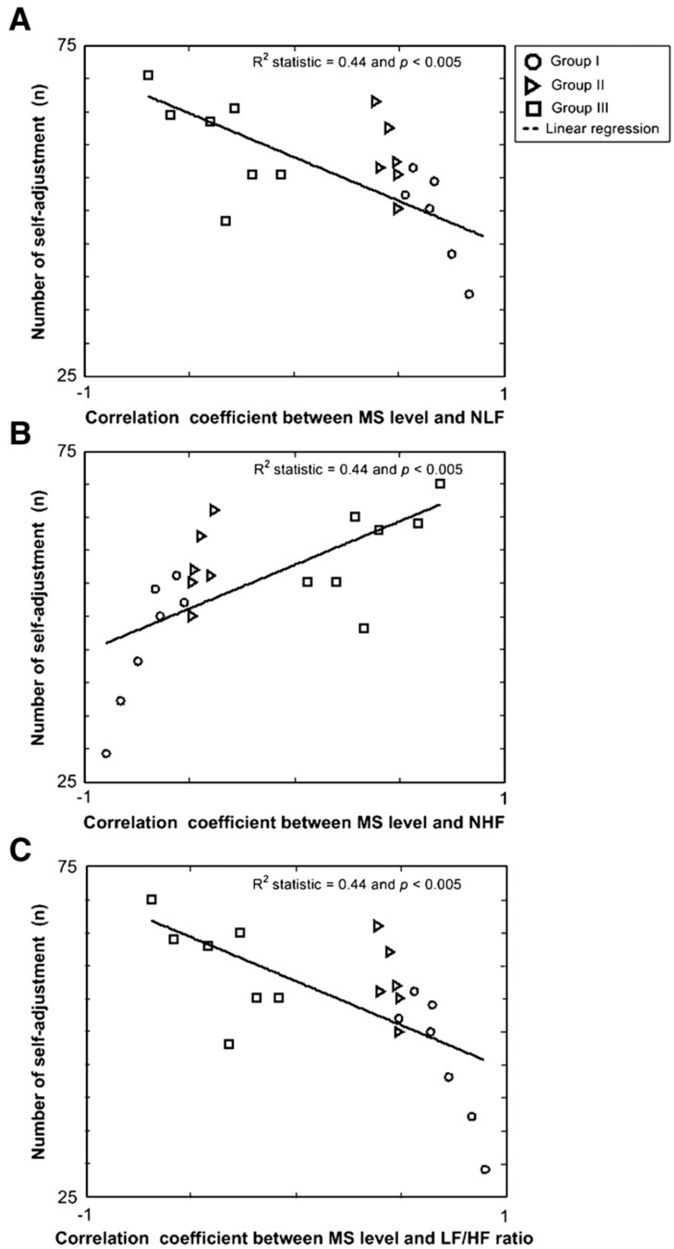

Fig. 7. Effects of self-adjustments on the correlation coefficients between the MS levels and the NLF (A), NHF (B) and LF/HF ratio (C). Each symbol represents an individual subject in Group I (○), Group II (△) and Group III (□; *x*-axis: correlation coefficient; *y*-axis: number of self-adjustments). The linear regression (solid lines) of the NLF (A), NHF (B) and LF/HF ratio (C) are shown for comparison. Note the number of self-adjustments altered the correlation coefficients between MS and the HRV indices (R^2 statistic = 0.44 and $p<0.005$; by the simple linear regression).

self-adjustments increased. All of the above findings suggested that one needs to take into account or control for self-adjustments in future research that assesses the HRV indices during motion sickness.

Among these self-adjustments, swallowing can cause phase resetting of respiratory rhythm and airway changes (Paydarfar et al., 1995; Cichero, 2006). Retching has similar effects on shaping respiration patterns. During retching, the airway is closed by the glottis to protect the airway from gastric acid (Cichero, 2006). Animal studies also showed that the pulmonary ventilation almost stopped during retching (Fukuda and Koga, 1993). During the retching phase, the inspiratory outputs from the respiratory rhythmic generator neurons were largely suppressed, while the expiratory outputs of the expiratory and inspiratory–expiratory neurons changed to retching and expulsion activities (Fukuda and Koga, 1997). The effect of self-adjustments on the MS–HRV relationship might be attributed to the irregular respiration produced by the self-adjustments. Irregular respiration has been known to alter sympathovagal activities or the balance of the autonomic nervous activities as reflected in HRV (Roach et al., 2004; Jerath et al., 2006; Grossman and Taylor, 2007; Pinheiro et al., 2007; Graham et al., 2009). The relationship between MS and sympathovagal activities was in turn altered. However, it remains inconclusive whether the MS–HRV relationship was only disturbed by the irregular respiration directly or indirectly induced by the self-adjustments and to what extent the MS–HRV relationship can be altered by the irregular respiration. Therefore, more studies need to include other psychophysiological measurements (e.g., a piezo-electric respiration belt for measuring the respiration or facial and neck electromyography signals for measuring the muscle activities of the face and neck) to carefully determine the role of the self-adjustments on the MS–HRV relationship and their underlying mechanisms.

4.3. MS levels decline prior to the end of the MS-induction winding-road session

Seven of the twenty subjects (35% of subjects) reported that their subjective MS levels declined prior to the end of the winding-road session (Fig. 3). We speculated that this decline might be caused by the subjects' active self-adjustments to relieve their MS symptoms. For example, the video images showed that subject 1 began to change her respiration approximately 5 min before her maximal MS level, which occurred 29 min after entering the winding-road session. Subsequently, the NLF and the LF/HF ratio decreased and the NHF increased 2 min after the respiration adjustments. The MS level decreased 3 min after the HRV indices changed. These results of this study empirically suggest that both the subjective MS levels and the physiological signals are sensitive to the self-adjustments. The results of a simple linear regression also demonstrate that self-adjustment could alter the relationship between the MS levels and the HRV indices.

4.4. Implications of this study

In literature, the relationship between the MS levels and HRV indices was controversial. Some studies suggested that the changes of HRV indices were related to degrees of MS (Gianaros et al., 2003; Holmes and Griffin, 2001; Yokota et al., 2005), but others reported that the HRV indices did not correlate with the MS levels at all (Beckers et al., 2006; Bos and Bles, 1998; Ohyama et al., 2007; Peng et al., 2007). The discrepant results were just simply attributed to the large inter-subject variations or the variations of the MS induced methods used in the literature. The goal of this study is to confirm the MS–HRV relationship and to investigate the possible reasons causing the controversial results in the literature. The results of this study not only confirmed the MS–HRV relationship but also provided new insights into the effects of self-adjustments on the MS–HRV relationship. Specifically, the results demonstrated that the MS levels increased along with the increases in the NLF values and the LF/HF ratios, whereas the NHF values decreased along with increases in the severity of MS. The self-adjustments largely accounted for the subjects who had zero or negative correlations between MS and the HRV indices. The so-called "large inter-subject variations" might be partially attributed to the self-adjustments used by individuals to ease their discomfort during the MS induction. The present findings also suggested that the HRV indices might be informative for objectively assessing the MS levels without interrupting the experiments and subjects in future MS studies.

Although the results of this study clearly showed the effects of the self-adjustments on the MS–HRV relationship, the underlying mechanism for how the self-adjustments alter the MS–HRS relationship remains unclear. More studies are required to better understand the neural mechanisms of MS, which might lead to new training paradigms or treatments to prevent or reduce the MS that is induced by a moving vehicle.

5. Conclusions

In summary, the present study showed that MS symptoms increase sympathetic activity and decrease parasympathetic activity, which were indexed by the HRV. However, this relationship could be altered by the self-adjustments that were used to relieve the discomfort of MS. This study not only provides evidence regarding MS–HRV relationship but also provides new insights and directions for further studies in exploring the neural mechanisms of MS and developing the new treatments for reducing or preventing the MS induced by a moving vehicle.

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