Chapter 7

Is SIC-susceptibility related to otolith asymmetry?

A functional asymmetry between the left and right otoliths has long been thought to contribute to an astronauts susceptibility to SAS. This hypothesis is verified using SIC as a ground based model for SAS. To that end, vestibular asymmetries (from a semicircular canal or otolith origin) were investigated in a group of 15 subjects for whom SIC susceptibility had been established. SIC susceptible subjects showed a higher degree of utricular asymmetry, but this parameter alone did not discriminate between the susceptible and the un-susceptible group. However, when otolith parameters were combined with semicircular canal parameters in a single regression model, the two groups could be perfectly separated. This implies that SIC susceptibility can be predicted based on vestibular parameters.

The previous chapters showed that, although there was a clear distinction between subjects as it comes to SIC susceptibility, this distinction was not observed in the ocular orienting responses. This chapter addresses the question whether the susceptible subjects can be discriminated from non-susceptible subjects on the basis of vestibular function. It was first thought that susceptibility to SAS could be predicted from susceptibility to other forms of Earthly motion sickness, but these attempts failed (e.g., Graybiel 1980; Homick et al., 1987; Oman et al., 1986). That susceptibility to SAS is related to vestibular function was

suggested by the so-called "otolith asymmetry hypothesis" (Baumgarten & Thümler, 1979; Von Bechterew, 1909). It was argued that a functional asymmetry between the left and right otoliths might contribute to susceptibility to SAS in astronauts. It was shown in 1969 by Yegorov amd Samarin that the otolithic pairs in fish (having an otolithic system homologous of that of humans), can actually be very different in size and weight (in Von Baumgarten & Thümler, 1979). While these asymmetries may be centrally compensated during normal life on Earth, they become unmasked in novel gravitational environments (like microgravity), where the compensation is inadequate. Such a misbalance within the otolith system would lead to the conflict causing motion sickness.

In humans, the only relatively pure indicator of otolith function is ocular counter roll (OCR). Vogel & Krass (1986) reported that the SL−1 crew member most prone to SAS during orbital flight also showed a marked asymmetry between OCR-gain in response to rightward and leftward body tilt before flight (see also Diamond & Markham, 1988). Young & Sinha (1998) report that all SLS−2 crewmembers had a symmetric ICR response to left- and rightward body tilt preflight, but showed a marked asymmetric response on the first day after return. They do not report upon a relationship with SAS-susceptibility. In addition, a relationship between gain asymmetry and SAS-susceptibility was not observed in a later study (Diamond et al, 1990). Instead, Diamond & Markham (1991) proposed that an otolith asymmetry would be observable during the novel G-states of parabolic flight as it would elicit a gravity dependent asymmetry in the torsional position of the right and left eye. In 13 astronauts they calculated a so-called level of torsional disconjugacy during parabolic flight (i.e., the left-right difference in 1.8 G relative to the left-right difference in 0G), and related this to the astronauts' individual susceptibility to SAS. Astronauts who had not been suffering from SAS during orbital flight appeared to have lower disconjugacy scores and vice versa (Diamond & Markham 1991; Markham & Diamond, 1992; 1993). A drawback of the procedures mentioned above is

that the otoliths were always stimulated *bilaterally*, making it difficult to discriminate directly between right and left otolith function. With the development of tests for the *unilateral* assessment of otolith function, it became possible to evaluate the otolith-asymmetry hypothesis in more detail.

Unilateral *utricular* function can be evaluated using eccentric centrifugation (Clarke et al., 1996; 1998; 2001; 2003; Wetzig et al., 1990; Wuyts et al., 2003). This is a paradigm using high speed vertical axis rotation, while changing the location of the rotation axis relative to the centre of the head. When the axis of rotation is aligned with one of the utricles the contra-lateral utricle is exposed to centrifugal acceleration, while the ipsilateral is not. The centrifugal acceleration tilts the gravito-inertial acceleration away from the vertical, inducing ocular counterrolling (OCR). Utricular asymmetry can thus be assessed by comparing the OCR elicited by both left and right utricular stimulation.

Unilateral *saccular* function can be assessed by recording vestibular evoked myogenic potentials (VEMPs, Colebatch et al, 1994). VEMPs are averaged inhibitory responses of the tonically contracted sternocleidomastoid muscle (SCM), and result from stimulating the saccule through loud acoustic stimuli. The VEMP waveform is biphasic, with a positive peak after 13 ms (*p13*) and a negative peak after 23 ms (*n23*). A saccular asymmetry would result in a difference between the peak-to-peak amplitude during rightward and leftward stimulation.

The otolith asymmetry-hypothesis was reinvestigated using sustained centrifugation as a ground based model for SAS. To that end, a group of subjects was selected that previously participated in one of the centrifuge-studies and for whom the susceptibility to SIC had been assessed. VEMPs were recorded to assess saccular asymmetry, while utricular asymmetry was tested through unilateral centrifugation. Originally, the latter test applied a semi-static trapezoid translation profile, where the rotation axis of the chair remained aligned with one of the utricles for a period of 30 s before translating to the other side (Wuyts et al., 2003). The current study used a novel sinusoidal translation profile, that has shown to generate

more robust responses (Wuyts et al., in preparation). A new mathematical model was developed to analyse these data, described in the method section. In addition to the two otolith tests, semicircular canal function was assessed through standard electro-nystagmographic procedures.

METHODS

15 Dutch subjects from the Soesterberg region (mean age 27, SD=7.8) volunteered to participate in this experiment and gave written informed consent. They were selected from a pool of 67 subjects that participated in one of the previous centrifuge-experiments, in which their susceptibility to SIC was assessed (see Chapters 1 and 2 for procedures) Seven of the 15 subjects were susceptible to SIC, whereas eight were not. The study-protocol was approved by the Medical Ethical Board of the Antwerp University Hospital.

Vestibular testing took place in the Antwerp University Research center for Equilibrium and Aerospace (Belgium). Apart from the unilateral assessment of otolith function (see below), hearing sensitivity was measured (Green, 1978), and a standard electro-nystagmography (ENG) protocol was performed to evaluate the unilateral functionality of the horizontal semicircular canals.

Testing of the horizontal semicircular canals

Standard electro-nystagmographic recording techniques were used for the evaluation of the horizontal semicircular canal function (Van der Stappen et al., 2000). The ENG test battery consisted of the recording of spontaneous nystagmus, followed by tests for gaze-evoked nystagmus, saccades, optokinetic nystagmus, smooth pursuit and positional nystagmus (Dix Halpike manoeuvre). Possible asymmetries between the left and right horizontal semicircular canals were assessed by a caloric test. During this test both ear canals were consecutively irrigated with warm (44°C) and cold (30°C) water for 30 seconds with a volume of 180

cc. Warm water in the right ear (WR) and cold water in the left ear (CL) both evoke nystagmus with fast phases to the right, whereas warm water in the left ear (WL) and cold water in the right ear (CR) both evoke nystagmus with fast phases to the left. Labyrinth preponderance (LP_{SCC}) was calculated by Jonkees' formula, based on the maximum slow phase velocities:

$$LP_{SCC} = \frac{(WL + CL) - (WR + CR)}{WL + CL + WR + CR} \tag{7.1}$$

where a positive value indicates a preponderance for the left labyrinth. The sum of the responses to the four irrigations (i.e., the numerator of Eq. 7.1, denoted by S_{SCC}) was taken as a measure for the total responsiveness of the horizontal semicircular canals.

The angular yaw VOR was measured during sinusoidal vertical axis rotation in total darkness with a maximum velocity of 50°/s and with a frequency of 0.05 Hz. Both head position and slow phase velocity (SPV) were described by a sine-function, where the offset in SPV determines the directional asymmetry (indicating that the SPV is higher in one movement-direction than the other). VOR gain was defined as the ratio of the SPV over head velocity.

Testing the saccules

Unilateral saccular function was assessed by the VEMP-test, as described by Vanspauwen et al (2006a, 2006b). After cleansing the skin with an impedance lowering gel, Ag/AgCl surface electrodes (Blue Sensor, Ambu), were placed on the medial portion of the contracted sternocleidomastoid muscle SCM' muscle belly (negative electrodes), the reference electrode on the upper part of the sternum and the ground electrode on the forehead. The subject was seated upright, with the head pitched forward over about 30°. Baseline contraction of the (SCM) was obtained by pressing the jaw against the hand-held inflated cuff of a blood pressure manometer. Because the VEMP response amplitude is dependent

on the SCM contraction level (Colebatch et al, 1994; Lim et al., 1997; Robertson & Ireland, 1995), care was taken to keep the contraction level of the SCM constant throughout the trial. To that end, the cuff pressure could be monitored by subject and investigator and the subject was to maintain a steady level throughout the trial. An auditory evoked potential system (Nicolet Viking) equipped with EMG-software was used to record the responses. Prior to the actual VEMP measurement, mean rectified voltage (MRV) values were recorded in this way, over a period of 15 s, as an indicator of SCM contraction level. Subsequently two series of 100 tone bursts (frequency 500 Hz; loudness 95 dBnHL; repetition rate 5.1 Hz) were presented unilaterally through insert earphones while averaging the resulting biphasic VEMP responses. During the VEMP recording, the cuff method was used at the same pressure level as during the MRV measurements. Peak-to-peak amplitude (*p13-n23,* see Figure 7.1) and absolute latencies (*p13, n23*) were obtained from the average response of the two series. The peak-to-peak amplitude was divided by the mean MRV value (as measured prior to the VEMP recording) to correct for the contraction level of the SCM. The whole procedure was performed separately for the left and right SCM.

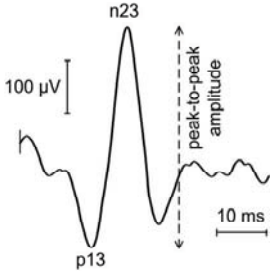

Figure 7.1: Example of a VEMP recording, with the negative peak, p13, and the positive peak, n23, indicated.

To determine saccular asymmetry, an asymmetry-factor ASF_{SAC} was

defined as:

$$ASF_{SAC} = \frac{|A_S - A_D|}{A_S + A_D} \tag{7.2}$$

where A denotes the corrected peak-to-peak amplitude, with the subscript S for *sinister* (left) and D for *dexter* (right). A_S and A_D are both positive so ASF_{SAC} ranges between 0 (perfect symmetry) and 1 (complete unilateral loss).

Testing the utricules

Utricular function was assessed by unilateral centrifugation (UC). The subject was seated in a vertical axis rotating chair (Neurokinetics, USA) and secured with a five-point belt. The head was stabilised with a head-rest and three flexible arms (Mitutoyo) pressing against the forehead. Eye movement recordings were made by 3D video-oculography (VOG)[11] at a sampling frequency of 50 Hz. During the measurement, the subject was instructed to look at a chair-fixed fixation light, presented at a distance of 1 m. At the beginning of the trial, the axis of rotation was aligned with the centre of the head and the chair was accelerated with 3°/s^2 to a constant velocity of 400°/s. Then, after a period of 90 s at this velocity, the chair was sinusoidally translated along the inter-aural axis at a frequency of 0.013 Hz. Maximum displacement was 4 cm to either side. Measured at the centre of the head, this induced a maximum interaural acceleration of 1.95 m/s^2 (=0.2 G), which is equivalent to a tilt of the gravito-inertial acceleration (GIA) of 11.2°. After 4 cycles (equivalent to 307.7 s) the rotation axis was again aligned with the centre of the head and the chair was brought to a stop with a deceleration of 2.5°/s^2. The protocol is depicted in Figure 7.2A-C, together with an example of the OCR-response (Figure 7.2D). The whole test was performed in the dark, with only the fixation light visible.

[11] The VOG-system used was developed by the Antwerp University Center for Equilibrium and Aerospace, based on a prototype by Kingma et al. (1995, 1997)

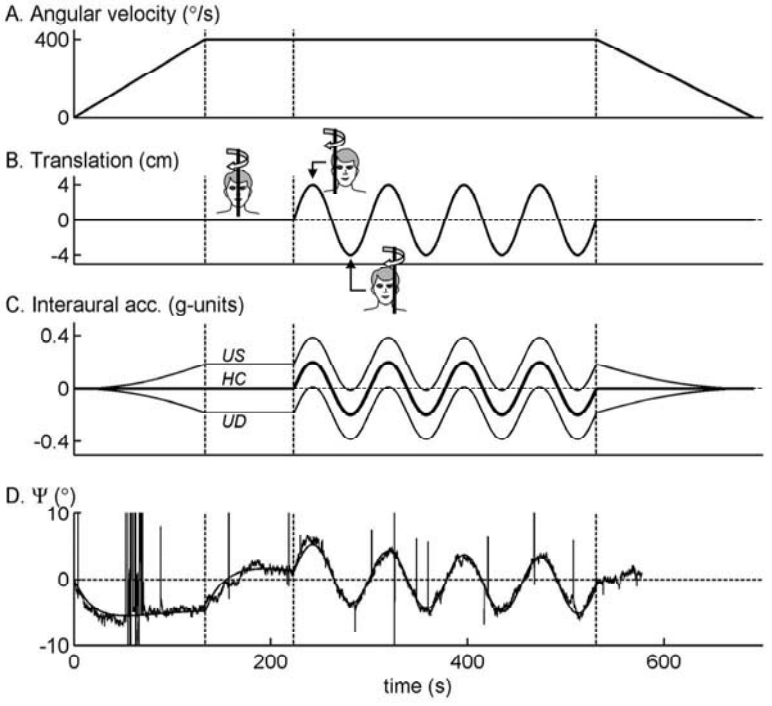

Figure 7.2: Unilateral centrifugation. A: Angular velocity profile. B: Interaural translation profile. C: Centripetal acceleration (in g-units) at the level of the left utricle (US), right utricle (UD) and head centre (HC). D: Example of an OCR response (Ψ). Note that the start (t=0 s) and stop (t=133.3 s) of angular yaw-acceleration of the chair elicit an OCR response that is still present at the start of translation (t=223.3 s). The fit of the model described by Eq. 7.3 - 7.8 is overlaid.

Modeling of the ocular response during unilateral centrifugation

Ocular responses were fitted to a mathematical model to determine the level of utricular asymmetry. Figure 7.2D clearly shows that both the angular acceleration of the chair and the lateral translation induce an OCR response. Most likely, only the part of the response induced by lateral translation (centripetal acceleration) can be attributed to the utricles, while the angular acceleration induced component has been attributed to the

semicircular canals (Smith et al., 1995). In order to isolate the utricular response, it is necessary to include the angular acceleration induced contribution in the model, because it has not died out fully at the start of translation. Thus, the total OCR response (Ψ) can be described by:

$$\Psi = \Psi_{\alpha} + \Psi_{u} \tag{7.3}$$

where the subscript u represents the utriclar contribution that is related to the centripetal acceleration, and α the response related to the yaw angular acceleration.

To investigate the dynamics of the component Ψ_{α}, some trials were recorded using the velocity profile of Figure 7.2A, but without the translation (see Figure 7.3). When the left and right utricles are assumed equally sensitive to centripetal acceleration the net utricular contribution equals zero (see Figure 7.2C), leaving only the semicircular canals to contribute to OCR. The OCR-response showed characteristics that resembled those of the slow phase velocity of horizontal nystagmus during vertical axis acceleration. It contained a velocity storage component (Raphan et al., 1979) that prolonged the effective time constant of the response, and an adaptation component, accounting for the gradual decay during continuation of the acceleration (Malcolm & Melvill-Jones, 1970; Young & Oman, 1969).

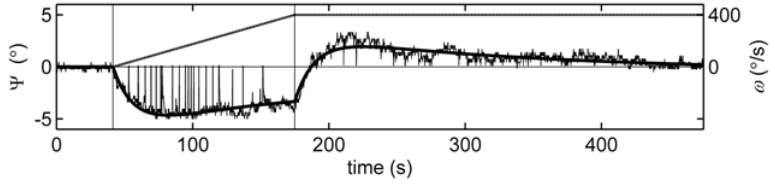

Figure 7.3: Example of an OCR response (Ψ) during acceleration of 3°/s² to 400°/s. The velocity profile is indicated by the dotted line (abscissa on the right). The frequent spikes in the first part of the data are due to eye blinks. The OCR-pattern shows a clear response to the start and stop of acceleration, indicated by the vertical lines. The fit of Eq. 7.5 is overlaid (A_{α}= 0.4, k=0.7, τ_C= 7.4 s, τ_A = 173.9 s).

Combining these properties with a first order model of the cupular dynamics yielded the following transfer function: (Laplace notation, see also Robinson 1981; Furman et al., 1989):

$$\frac{\Psi_\alpha(s)}{\omega_{head}(s)} = A_\alpha \cdot \frac{1}{1-k} \cdot \frac{\tau_A s}{\tau_A s + 1} \cdot \frac{\tau_C s}{(\tau_C / 1-k)s + 1} \tag{7.4}$$

where A_α is a gain factor, τ_A the adaptation time constant, and τ_C the cupular time constant. The factor k assumes a value between 0 and 1 and accounts for velocity storage. The velocity storage time constant, τ_{VS}, is then given by:

$$\tau_{VS} = \frac{\tau_C}{1-k} \tag{7.5}$$

Transforming Eq. 7.4 to the time domain yields the following equation for Ψ_α that consists of a sum of four exponentials, two for the start of angular acceleration and two for the stop of angular acceleration:

$$\Psi_\alpha(t) = A_\alpha \cdot \left(\frac{\tau_C \cdot \tau_A}{\tau_C - \tau_A + k \cdot \tau_A} \cdot \left(e^{\frac{-t}{\tau_A}} - e^{\frac{(-1+k)\cdot t}{\tau_C}} \right) \right) + \ \ldots \tag{7.6}$$

$$A_\alpha \cdot K_1 \cdot \left(\frac{\tau_C \cdot \tau_A}{\tau_C - \tau_A + k \cdot \tau_A} \cdot \left(e^{\frac{-(t - t_{stop\_acc})}{\tau_A}} - e^{\frac{(-1+k)\cdot(t - t_{stop\_acc})}{\tau_C}} \right) \right)$$

The second part of Eq. 7.6 only contributes to the response when the chair has reached its final angular velocity (t_{stop_acc}). K_1 is thus an inclusion parameter, where $K_1 = 0$ as $t<t_{stop\_acc}$ and $K_1 = 1$ as $t \geq t_{stop\_acc}$.

The utricular induced OCR is assumed proportional to the magnitude of the interaural acceleration:

$$\Psi_u(t) = \alpha_{us} \cdot \omega(t)^2 \cdot \left(R_u + R(t)\right) + \alpha_{ud} \cdot \omega(t)^2 \cdot \left(-R_u + R(t)\right) \tag{7.7}$$

where the first part of the right-hand side describes the contribution of the left utricle (subscript *us*), and the second part describes the contribution of

the right utricle (subscript *ud*). The parameter α is a proportionality constant, and $\omega(t)$ is the angular velocity of the chair. R_u is the distance between the utricle and the centre of the head, being positive for the left side and negative for the right side. The utricles are assumed to lie symmetrically around the centre of the head (Nowé et al, 2003) with the mean inter-utricular distance equal to 7.45 (SE 0.08) cm for males and 6.99 (SE 0.06) cm for females (Nowé et al, 2003). $R(t)$ is the distance between the axis of rotation and the centre of the head. It equals 0 when the chair is on centre, and during the translation-phase $R(t)$ is given by:

$$R(t) = R_{\max} \cdot \sin(2\pi f(t - dt)) \tag{7.8}$$

where R_{max} is the translation amplitude (0.04 m) and f the translation frequency (0.013 Hz). The term dt is incorporated to account for possible phase differences between the actual translation of the chair and the ocular response. Combining Eq. 7.7 and 7.8 yields the following expression for Ψ_u:

$$\begin{aligned}\Psi_u(t) = &\left((\alpha_{us} - \alpha_{ud}) \cdot \omega(t)^2 \cdot R_u\right) + \ldots \\ &K_2 \cdot \left((\alpha_{us} + \alpha_{ud}) \cdot \omega(t)^2 \cdot R_{\max} \cdot \sin(2\pi f(t - t_{start\_trans} - dt))\right)\end{aligned} \tag{7.9}$$

where $K_2 = 0$ for $t<t_{start\_trans}$ (i.e., the start of lateral translation) and $K_2 = 1$ for $t \geq t_{start\_trans}$.

The total OCR-response can thus be described by combining Eq. 7.6 and 7.9. Figure 7.4 shows the four components of the model: the response to the start of angular acceleration, the response to the stop of angular acceleration, the response from the left utricle to chair translation and the response of the right utricle to chair translation. The sum of these four components equals the measured OCR response.

A utricular asymmetry is characterized by the values of α_{us} and α_{ud}. When these values are equal, both utricles are equally sensitive, and when they differ in magnitude, an asymmetry exists. A utricular asymmetry factor was defined as:

$$ASF_u = \frac{|\alpha_{us} - \alpha_{ud}|}{\alpha_{us} + \alpha_{ud}} \tag{7.10}$$

Again, α_{us} and α_{ud} are both positive so ASF_U ranges between 0 (perfect symmetry) and 1 (complete unilateral loss). The offset of the sine function (i.e., first part of Eq. 7.9) was taken as an additional measure for utricular asymmetry. Note that the sensitivity of the utricles is also characterized by α_{us} and α_{ud}: higher values indicate a larger sensitivity. The amplitude of the response (A_u, derived from the second part from Eq. 7.9) was taken as a measure for utricular sensitivity. Other parameters of interest were the maximum amplitude of Ψ_α, and the time constants τ_C, τ_A, and τ_{VS}.

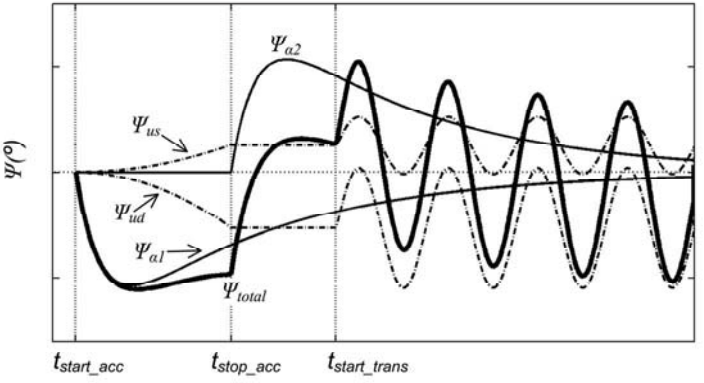

Figure 7.4: Components of the model to fit the OCR data, for the data presented in Figure 7.2D. t_{start_acc}=start of angular acceleration; t_{stop_acc}=stop of angular acceleration (constant velocity); t_{start_trans}=start lateral translation; Ψα1=response to first angular acceleration step; $\Psi_{\alpha 2}$=response to second angular acceleration step; Ψ_{us}=response from left utricle; Ψ_{ud}= response from right utricle; Ψ_{total}= sum of all components. Model parameters are τ_C=4.4 s; τ_A=144.6 s; A_α=0.35; k=0.80; dt=0.42 s; α_{us}=0.70; α_{ud}=1.45. Note that in this case the left utricle is less sensitive than the right utricle.

The model of Eq. 7.6 and 7.9 was fitted to the mean ocular torsion position data (left + right eye) to obtain individual values for different

parameters. An example of a model-fit was already shown in Figure 7.2D. By using the average data of the two eyes the model does not account for prevalence or preponderance, that is, a dominant utricular impact on the ipsilateral eye (Wetzig et al., 1990). However, earlier studies showed that the responses of both eyes are reasonably equivalent in normal subjects (Clarke & Engelhorn, 1998; Wuyts et al., 2003). Close inspection of the data showed that this was also the case in the present data.

RESULTS

Reliable responses for utricular and saccular parameters were obtained in 12 subjects. In two of those 12 subjects the OCR data of the acceleration phase of the UC-test contained too many eye blinks to obtain reliable parameters for the first part of the response (τ_C, τ_A, τ_{VS}, and max. Ψ_α). For these subjects utricular parameters were obtained from a fit (Eq. 7.9) on data of the last two translation cycles only. In one subject the caloric test had to be aborted due to severe nausea. The VOR-data was not used for further analysis, because the gain was found to be below the normal range (Van der Stappen et al., 2000) in seven of the 15 subjects. The most plausible explanation for the low VOR gain would be fatigue, caused by the busy test-schedule and the journey from Soesterberg to Antwerp.

Evaluation of the model assessing utricular function

The model describing the ocular response of the UC-test provided an adequate description of the data, the R^2 values ranged between 0.88 and 0.92. More imporant, the utricular parameters α_{us} and α_{ud} that determine both the utricular asymmetry (ASF_U) and utricular sensitivity (A_u) could be estimated adequately. Individual parameter values and confidence intervals are listed in Table 7.1. This was different for the parameters describing the angular acceleration induced part of the response. Confidence intervals of these parameters (time constants τ_C, τ_A, and τ_{VS}) were an order of magnitude larger than the actual parameter values.

Because the overall fit of the model to he data was good, this means that the same ocular response pattern could be obtained using different combinations of time constants. This was also verified by model simulations. Thus, although the model gave a good description of the angular acceleration-induced response, it did not provide a reliable estimation for individual time constant values. Therefore these values were ignored in further analysis.

TABLE 7.1

Individual values for the estimated utricular parameters α_{us} and α_{ud} and 95% confidence intervals (CI)

Subject	α_{us}	CI	α_{ud}	CI
1	0.846	[0.814, 0.878]	0.122	[0.090, 0.154]
2	0.584	[0.582, 0.587]	0.301	[0.298, 0.303]
3	0.370	[0.366, 0.373]	1.020	[1.016, 1.022]
4	0.530	[0.526, 0.534]	0.549	[0.544, 0.553]
5	0.609	[0.602, 0.616]	1.096	[1.090, 1.101]
6	0.058	[0.054, 0.063]	1.209	[1.205, 1.213]
7	0.342	[0.339, 0.345]	0.584	[0.581, 0.586]
8	0.154	[0.150, 0.157]	0.755	[0.752, 0.758]
9	0.492	[0.488, 0.496]	0.445	[0.441, 0.449]
10	0.279	[0.253, 0.295]	0.878	[0.862, 0.903]
11	0.766	[0.746, 0.787]	0.382	[0.361, 0.402]
12	0.216	[0.218, 0.238]	0.696	[0.677, 0.695]

Differences between SIC-susceptible and non-susceptible subjects

Table 7.2 provides descriptive values for the relevant vestibular parameters from all vestibular tests. Note that the values for the time constants are also included in Table 7.2, but that these have to be treated with care as mentioned above.

TABLE 7.2
*Descriptive statistics for the relevant vestibular parameters. Parameters marked with * show differences between the SIC-susceptible group and the non-susceptible group (p<.1)*

		n	mean	SD	min	max
VOR	Gain	15	0.41	0.25	0.12	1.04
Caloric test	Abs. directional asymmetry (°/s)	9	5	4	2	11
	* Responsiveness, S_{SCC} (°/s)	14	86	34	47	169
	Abs. labyrinth preponderance, LP_{SCC}	14	0.10	0.06	0.02	0.20
VEMP-test	*p13* (ms)	12	15.8	1.4	14.2	19.2
	n23 (ms)	12	23.6	2.0	21.0	28.4
	Baseline MRV value (μV)	12	86.3	27.6	43.1	131.6
	Peak-to-peak amplitude VEMP	12	104.1	63.6	28.6	278.6
	Amp. corrected for MRV	12	1.3	0.8	0.3	3.9
	Abs. saccular asymmetry, ASF_{sac}	12	0.19	0.12	0.04	0.44
UC-test	Cupular time constant, τ_C (s)	10	5.1	0.8	4.0	6.5
	Adaptation time constant, τ_A (s)	10	228.0	169.7	77.0	671.1
	Velocity storage time constant, τ_{VS} (s)	10	83.1	119.4	11.1	400.7
	Max. amplitude Ψ_ω,(°)	10	2.1	1.3	0.6	4.5
	* Amplitude Ψ_u, A_u (°)	12	2.1	0.5	1.7	3.3
	Abs. offset Ψ_u (°)	12	0.7	0.5	0.1	2.1
	* Abs. utricular asymmetry, ASF_u	12	0.43	0.25	0.05	0.91

Of the subjects selected for this study, seven were susceptible to SIC, while the other eight were not. Non-parametric statistics (Mann-Whitney U test) were used to investigate differences between the groups. Although none of the parameters showed differences between the groups that were significant at the $p<.05$ level, four of them showed significant differences at the $p<.1$ level. Regarding the utricular parameters, the SIC susceptible group showed a higher level of utricular asymmetry (ASF_U, $p=.065$), and a higher amplitude of the utricular response ($p=.093$). In addition, the caloric responsiveness of the semicircular canals, S_{SCC}, was higher in the SIC-susceptible group ($p=.059$). These differences are also depicted in Figure 7.5. The VEMP test reveiled no differences between the SIC-susceptible group and the non-susceptible group for saccular paramterers.

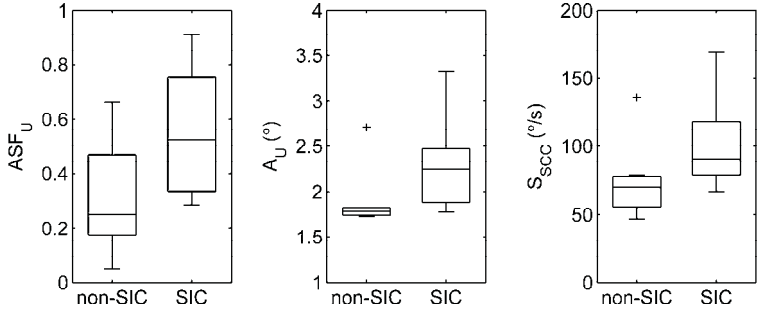

Figure 7.5: Box plots of the parameters that differed between the SIC-susceptible group and the non-susceptible group (p<.01): Utricular asymmetry factor (ASF_U) amplitude of the utricular response (A_u), and caloric responsiveness (S_{SCC}). Boxes represent the upper and lower quartile range, whiskers represent the extremes within 1.5 times the interquartile range. Outliers are indicated by the + sign.

Classification of subjects

Logistic regression analysis was performed to determine whether the subjects could be correctly classified as being SIC-susceptible or not. The regression model was of the form:

$$y = \frac{e^k}{(1+e^k)}, \text{ with } k = a_1 \cdot x_1 + a_2 \cdot x_2 + \ldots + a_n \cdot x_n + c \qquad (7.11)$$

where y ranges between 0 and 1, x denotes the different parameters, a denotes the regression coefficients, and c is a regression-contant. Although absolute otolith asymmetry differed significantly between the SIC-susceptible and the non-susceptible group, it had not enough discriminating power to classify all subjects correctly ($\chi^2(1)=3.4$, $p=.065$): the range of observed values overlapped (see also Figure 7.5) and consequently, four out of 12 subjects were misclassified. Including semicircular canal parameters in the model significantly improved classification. Because of the small number of subjects having a full data set on all parameters stepwise regression could not be performed. Instead, regression models were evaluated using different combinations of utricular (UC-test) and semicircular canal parameters (Caloric test). With a combination of utricular asymmetry (ASF_u), utricular responsiveness (A_U), semicircular canal asymmetry (LP_{SCC}) and semicircular canal responsiveness (S_{SCC}) a perfect classification of subjects could be obtained ($\chi^2(4)=15.2$, $p=.004$) Regression coefficients are shown in Table 7.3.

TABLE 7.3
Parameters of the logistic regression model

Parameter	Coefficient
A_u	206.5
ASF_u	371.1
S_{SCC}	1.7
LP_{SCC}	2672.4
Constant	–1133.4

DISCUSSION

The aim of the current study was to determine whether functional otolith asymmetries were related to SIC-susceptibility, as is suggested by the otolith-asymmetry hypothesis (Von Baumgarten & Thümler, 1979). The SIC-susceptible group indeed showed a higher level of utricular asymmetry than the non-susceptible group, which would be in favour of this hypothesis. Logistic regression analysis showed, however, that utricular asymmetry appears not to be the sole determinant of SIC-susceptibility. The finding that the SIC-susceptible group showed both a higher utricular gain and larger semicircular canal responsiveness to caloric stimulation suggests that the overall sensitivity of the vestibular system might also be contributing.

Prediction of SIC-susceptibility

Interestingly, combining the caloric test-parameters with the utricular test parameters in a single logistic regression model yielded perfect classification of the 12 subjects. This is a promising result, despite the fact that the data-set was too small to perform more advanced logistic regression techniques. It suggests that SIC-susceptibility can be predicted based on vestibular function parameters that address sensitivity and asymmetry of both the otolith and canal system. An important next step is to validate the model in a larger group of subjects. It is possible that a more accurate model can then be obtained using a different subset of parameters, possibly also including VOR-characteristics like gain and/or time constants. The current results, however, are already valuable in showing that utricular parameters alone are not sufficient to predict SIC-susceptibility.

The many attempts to predict SAS-susceptibility from susceptibility to other forms of motion sickness failed (e.g., Graybiel 1980; Oman et al., 1986; Homick et al., 1987) or did not specifically address SAS-

susceptibility as measured in flight (Lin & Reschke, 1987; Cloutier & Watt, 2006). Given the correlation between susceptibility to SIC and to SAS, it is expected that a logistic model as proposed above can also be applied as a predictor for SAS in astronauts. In this thesis it was argued that sustained centrifugation was the only possible ground-based paradigm to assess SAS-susceptibility, but now the use of unilateral vestibular testing may thus be added as an assessment method. Also valuable in this respect are the findings of Harm and colleagues (1998), who found that astronauts who showed a visually dominated frame of reference (i.e., who were more field dependent) were more prone to SAS during space flight than astronauts who showed a body-centric frame of reference. It would be interesting to investigate whether this personal preference is also related to vestibular function or whether it could attribute to the prediction of SAS-susceptibility.

Static vs. dynamic Space Motion Sickness

The otolith-asymmetry hypothesis has always been related to a static form of SAS, that did not require motion to elicit the symptoms (Von Baumgarten & Thümler, 1979; Von Baumgarten et al., 1981; Von Baumgarten, 1987). Although it has occasionally been reported that SAS can be experienced during rest (Graybiel, 1980), it is generally accepted that head and body movements are a prerequisite for the symptoms to occur (e.g., Graybiel, 1980; Oman et al., 1986; Thornton et al., 1987). Importantly, this dynamic component is also a prerequisite for the generation of SIC: in none of the centrifuge studies SIC was observed when the subject remained motionless after centrifugation. In fact, head movements were used to classify an individual as SIC-susceptible or not. The finding that, next to utricular parameters, also semicircular canal parameters varied between the SIC-susceptible group and the non-susceptible group is in line with this dynamic character of SIC. It also is in line with the fact that both systems are involved in spatial orientation: integration of semicircular canal and otolith signals is required to obtain

valid internal estimates of inertial acceleration and gravity, as was addressed in Chapter 1 and Chapter 6. Because the gravitational vertical plays a central role in the generation of motion sickness (Bles et al., 1998a), it is plausible that a disturbed interaction between the various parts of the vestibular system is involved in SIC and SAS.

Model to assess utricular asymmetry

The values obtained for the utricular parameters are partly dependent on the model used to fit the torsional position data in the angular acceleration phase of the test (Eq. 7.4). This model was based on the dynamics of the horizontal semicircular canal, given the resemblance between the torsional position response during yaw angular acceleration (i.e., with fixation) and the slow phase velocity of the horizontal nystagmus during angular acceleration (i.e., without fixation).

A semicircular canal basis for this torsional position response has also been suggested by Smith and colleagues (1995). They showed that the magnitude of this response is dependent on angular acceleration and is not related to the centripetal acceleration acting on the utricles, which makes a utricular origin unlikely. In agreement with this, the maximum net centripetal acceleration acting on the center of the head during angular acceleration was much smaller than during the translation phase of the UC-test, while the OCR-responses are of equal magnitude (i.e., compare max. Ψ_{SCC} with amplitude Ψ_{U}). In addition, the *tangential* acceleration acting on the utricles during yaw angular acceleration (≈0.0002G) is much smaller than the maximum centripetal acceleration of the translation phase (≈0.2G), indicating that the tangential stimulation of the utricles probably did not contribute to the response. Smith and colleagues also noted the correspondence of the torsional position response with the canal dynamics and suggested that the velocity-to-position integrator responsible for holding torsional eye position might receive input from the horizontal semicircular canal. However, the OCR-data show that the torsional position response and the horizontal velocity response are not

equivalent. Both the mean adaptation time constant and the mean velocity storage time constant for the OCR-response are much larger than generally observed for the horizontal slow phase velocity (i.e., 15-20 sec.; see e.g., Brown & Wolfe, 1969; Fernandez & Goldberg, 1971; Malcolm & Melvill Jones 1970; Bos et al. 2002). Nevertheless, with the model of Eq. 7.4 a good description of the data was obtained within the temporal range of the measurement, and, more importantly, the utricular parameters could be estimated adequately. To elucidate the exact mechanism of the angular acceleration induced torsional position response, further research is required.

Conclusion

The mathematical model developed to assess utricular asymmetry yielded an adequate description of the data, by incorporating both angular acceleration induced torsion responses and the linear acceleration induced torsion responses. In line with the otolith asymmetry hypothesis, SIC susceptible subjects showed a higher level of utricular asymmetry than unsusceptible subjects, but a proper classification of subjects could only be obtained using both utricular and semicircular canal parameters. This illustrates that the whole vestibular system is involved in SIC and demonstrates the role of – complex – interactions between its parts.