Chapter 6

The effect of sustained centrifugation on the spatial characteristics of velocity storage

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This chapter focuses on the effects of sustained centrifugation on the velocity storage (VS) mechanism, which is associated with the interaction between otolith and semicircular canal signals in the low frequency range. Recently it has been proposed that this VS mechanism plays a role in the discrimination of gravitational and inertial acceleration during dynamic mid-frequency head movements as well. The effects of sustained centrifugation found so far may therefore be related to inadequate processing of these vestibular signals. In humans, the VS mechanism is also responsible for the reorientation of the eye velocity vector (EVV) towards gravity during off-vertical optokinetic and vestibular stimulation. It was therefore investigated whether these spatial eye movement properties were affected after sustained centrifugation. To that end, yaw optokinetic nystagmus was recorded with the head erect and tilted to the side. The results indicated a reduction in the reorientation of the EVV following sustained centrifugation, which suggests a decrease in velocity storage activity.

This chapter tries to link the aftereffects of sustained centrifugation, like motion sickness and disorientation, to changes in canal-otolith interaction. More specifically, it focuses on a process called velocity storage (VS) which, as will be described below, appears to play a role in solving the tilt-translation ambiguity. As mentioned in Chapter 1, the tilt-translation ambiguity refers to the fact that inertial (i.e., translation) and gravitational acceleration (i.e., tilt) are physically indistinguishable.

The so called VS-mechanism or -integrator (Raphan et al., 1979) refers to a brain stem network with integrative properties that traditionally is believed to improve the dynamics of the angular vestibulo-ocular reflex (aVOR) at low frequencies. When rotating at a constant velocity, for example, it extends the duration of effective compensation for head movement by increasing the dominant time constant of the aVOR, as was also mentioned in previous chapters. The VS-integrator is also responsible for the dynamics of the nystagmus observed during and after optokinetic stimulation (Cohen et al., 1977; Cohen et al., 1981; Raphan et al., 1979). Nevertheless, several researchers suggested that, apart from these properties, the actual purpose of this network is to integrate multiple sensory signals to provide a spatially referenced estimate of head velocity (Angelaki & Hess, 1994; 1995; Jaggi-Schwarz et al., 2000), likely aimed at stabilizing gaze during locomotion (Dai et al., 1991; Solomon & Cohen 1992). The properties of the VS-integrator remained, however, associated with low frequency behaviour, outside the range of natural movements.

Interestingly, Green and Angelaki (2003, 2004) proposed a new role for the VS-integrator in spatial orientation. They suggested that its main function is to process (temporally integrate) spatially referenced extra-otolith information, necessary for the discrimination of gravitational and inertial acceleration (see Chapter 1). Thus, in order to generate appropriate responses, our central nervous system has to use additional (extra-otolith) information to distinguish between gravity and inertia. The temporal integration of angular velocity signals (e.g. originating from the semicircular canals) ensures the appropriate eye movements during combined translational and tilt movements.

The idea that angular velocity signals are necessary to discriminate tilt from translation is not novel (Mayne, 1974), and has been applied in many models for spatial orientation (e.g., Angelaki et al., 1999; Merfeld et al., 1993; 1999; Bos & Bles, 2002; Zupan et al., 2002). New is the idea that the required temporal integration could well be performed through the VS-integrator, as suggested by Green and Angelaki (2003; 2004). This would especially apply to movements in the mid-high frequency range (i.e., the range of natural movements), which opens up a new perspective for understanding the problems with spatial orientation induced by sustained centrifugation. These problems, in particular the occurrence of motion sickness, usually arise during mid- to high-frequency movements, and especially when head tilt is involved (Bles & De Graaf, 1993; De Graaf & De Roo, 1996; Bles et al., 1997). Interestingly, it has been demonstrated that VS-activity is related to motion sickness susceptibility: subjects showing a long aVOR time constant during vertical yaw axis rotation (horizontal aVOR) were found to be more prone to motion sickness than subjects showing shorter time constants (e.g. Bos et al., 2002; Cohen et al., 2003; Dai et al., 2003; De Wit, 1953; Quarck et al., 1998). In addition, Dai and colleagues (2003, Cohen et al., 2003) demonstrated a relationship between the *spatial* properties of VS and motion sickness induced by Coriolis stimulation. The spatial properties of VS emerge during rotation about an off-vertical axis, where the eye velocity vector (EVV) shows a tendency to align with gravity (e.g., Dai et al., 1991; Raphan & Cohen, 1989; Raphan & Sturm, 1991, see Cohen et al., 1999 for a review) instead of remaining aligned to the stimulus-axis. Dai et al. (2003) suggested that the misalignment between the EVV and the Earth vertical was responsible for the experienced motion sickness. They therefore proposed that VS is the critical element in the generation of motion sickness.

Given the proposed relationship between VS activity, the tilt/translation ambiguity and motion sickness, it was hypothesized that sustained centrifugation affects the VS mechanism, which, in turn, may be responsible for some of the phenomena observed after sustained centrifugation. There is already some evidence that VS is indeed affected by exposure to altered gravitational states. DiZio and Lackner showed in a series of experiments that the dominant time constant of the horizontal aVOR was reduced during the both the 1.8 and 0G phase of parabolic flight (1987; 1988; 1991; 1992). And, as was already mentioned in Chapter 3, sustained centrifugation (60 min at $3G_x$) also led to a reduction of this time constant (Groen, 1997), suggesting a reduction of velocity storage activity.

The current study focuses on the spatial properties of VS, that is, the tendency of the EVV to align with gravity. In humans this becomes apparent during horizontal optokinetic nystagmus (OKN) with the head tilted to the side: apart from a horizontal eye movement, a vertical component is often present as well (Arai & Cohen, 1999; Gizzi et al., 1994; Moore et al. 2005). This phenomenon is called cross-coupling. Although the resulting reorientation of the EVV is far from perfect (about 20% of the head tilt), the amount of reorientation can serve as a measure for the VS activity. Given the results of Groen (1997) mentioned above, sustained centrifugation was expected to reduce this effect of head tilt on EVV-reorientation.

For this study, OKN was recorded during optokinetic stimulation about the subject's yaw axis as a function of lateral head tilt, and it was investigated whether the responses were affected by sustained centrifugation. After showing that the amount of cross-coupling is reduced following sustained centrifugation, a model will be presented that relates the observed changes in cross-coupling with a decrease in the VS-contribution to the spatial orientation of the EVV. The discussion will finally elaborate on the possible consequences for spatial orientation.

METHODS

The assessment of velocity storage activity through the recording of optokinetic nystagmus was part of the experiment described in Chapter 3 (see Figure 3.4 for the design of this experiment). In short, 12 non-astronaut subjects were exposed to four different centrifuge conditions on four different days. The centrifuge conditions differed in G-load and duration and consisted of a 45 or 90 min. exposure to $2G_x$ or $3G_x$ (denoted by 2G45, 2G90, 3G45 and 3G90, respectively). Optokinetic nystagmus was recorded within 45 min. before and 30 min. after the centrifuge run. The centrifugation procedures have been described in Chapter 2.

Recording of optokinetic nystagmus

Binocular eye movements were recorded at a sampling rate of 100 Hz using a head-mounted video-based eye tracking device (ETD, Chronos Ltd, Berlin). The subjects were seated on a height-adjustable chair, placed in front of a backlit projection screen (110 by 150 cm). Viewing distance was 65 cm. Head position in space was fixed by means of a personal bite board, attached to a standard that could be placed in one of the desired head positions: erect, or tilted 45º to the left or right.

To drive horizontal eye movements while allowing vertical eye motion, the optokinetic stimulus consisted of a symmetrical vertical black and white stripe pattern that was projected in a circular field of view, extending over a viewing angle of 74º (see Figure 6.1). The centre of the stimulus area was always located straight ahead. Stripe width was 3º in all viewing angles, thus simulating a drum rotating about the subject's yaw axis. Edges of the stripes were blurred to minimize visual tracking. The pattern was always aligned with the head's yaw axis, and moved at 35º/s. The experiments took place in an otherwise darkened room.

Figure 6.1: The optokinetic stimulus in the three head tilt conditions. The pattern moved along the interaural axis, either from left to right or from right to left.

After positioning the subject in one of the three head tilt conditions a calibration was performed for the right and left eye separately.

Subsequently, a fixation dot was presented at the centre of the screen for 3 s, followed by 30 s of optokinetic stimulation. After that, the stimulus was switched off (thus leaving the subject in total darkness), while the eye movement recording continued for 10 s. Subsequently, the measurement was repeated with the pattern moving in the opposite direction. Tilt conditions (3) and stimulus direction (2) were presented in a random order, amounting to six trials per test (pre and post centrifugation) in total.

Data analysis: determination of the eye velocity vector

3D eye position (Fick angles) was obtained using dedicated software (Iris Tracker, Chronos Ltd, Berlin). Horizontal and vertical eye position was based on automatic pupil tracking, whereas the torsional position (rotation about the line of sight) was computed by polar cross correlation of iris segments (Clarke et al., 2002), as described in Chapter 5. The 3D eye velocity vector (EVV) was calculated from the eye position data and their time derivatives (Goldstein, 1980; Haslwanter, 1995). Yaw eye velocity (ω_z) was defined as the component generating left-right eye movements and pitch eye velocity (ω_y) as the component generating up-down eye movements. A right-handed, head-fixed frame of reference was used throughout, with the x-axis aligned with the straight ahead gaze, and the y-axis aligned with the inter-aural axis.

The amount of cross-coupling during OKN was characterized by the median orientation of the EVV relative to the stimulus axis (i.e. the head longitudinal axis, see also Figure 6.2). The first 10 seconds of each trial were disregarded from the analyses, to ensure full build up of velocity storage (Fletcher et al., 1990). After removing the saccades of the remaining 20s interval, the mean eye velocity per nystagmus beat was calculated from a linear fit on the raw eye velocity data. The orientation of the EVV was then defined as $\alpha = \text{atan}\left(\text{med}(\omega_y)/\text{med}(\omega_z)\right)$. For statistical analysis results of the left and right eye were averaged. OKN gain was defined as the median of ω_z divided by the stimulus velocity.

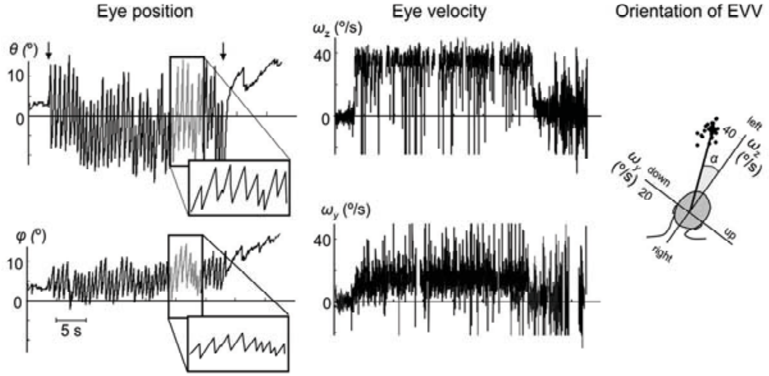


Figure 6.2: Example of a recording when the head was tilted to the right and the stripes were going from right to left. The left panel shows the horizontal (θ) and vertical (φ) eye position (Fick angles, where positive values indicate leftward and downward eye positions). The start ("lights on") and stop ("lights off") of the optokinetic stimulus are indicated by vertical arrows. The middle panel shows the corresponding components of eye velocity. The resulting orientation of the EVV (denoted by α) is shown in the right panel. Here, each dot represents the mean eye velocity of one nystagmus beat. The pitch-down component induces a reorientation of the EVV towards the spatial vertical. Note that downward eye movements result in EVV endpoints left of the z-axis.

RESULTS

An example of a recording is given in Figure 6.2 (head tilt to the right, stripes from right to left). At the start of the optokinetic stimulus (first arrow in upper-left panel of Figure 6.2) yaw eye velocity builds up almost immediately. A pitch-down component (i.e., cross-coupling) is also present, taking several seconds to build up. Due to this pitch component, the EVV shifts towards the spatial vertical (see Figure 6.2, right panel). When the stimulus is switched off (second arrow in upper-left panel of Figure 6.2) a small optokinetic after nystagmus (OKAN) is present. In the following section the data on cross-coupling during OKN is presented, reflecting the spatial properties of VS. Subsequently the second section presents a model describing these results, in order to quantify the effects found.

Cross-coupling during OKN

Figure 6.3 shows the average orientation of the EVV in the six experimental conditions as measured before and after centrifugation (3G90 condition). The other centrifuge conditions gave similar results. The EVV is expressed relative to the head yaw axis. A deviation of the EVV from the ordinate in Figure 6.3 indicates the presence of a pitch eye movement, i.e., cross-coupling.

Surprisingly, a small but significant amount of cross coupling is present when the head is erect: A pitch down eye movement is observed that is independent of the direction of the optokinetic pattern. This was consistent over all conditions and subjects and tilted the EVV away from the head yaw axis over an angle of 5.0° (mean over 192 observations, SD=4.0º, $t(11)=5.46$, $p=.0002$). Due to this component, the reorientation of the EVV caused by the lateral head-tilt is biased in the pitch-down direction, but it still induces an additional shift towards the spatial vertical: a downward eye velocity component was present when the stimulus velocity had an upward component with respect to gravity, and an upward eye velocity component was present when the stimulus velocity had a downward component relative to gravity. As such, the six conditions can be divided into three groups, based on the characteristics of the optokinetic stimulus velocity with respect to gravity (see also Figure 6.3): 'G-neutral' (stimulus velocity axis is aligned with gravity), 'Against-G' (stimulus velocity axis is tilted away from the Earth vertical, having an upward component with respect to gravity) and 'With-G' (stimulus velocity axis is tilted away from the Earth-vertical, having a downward component with respect to gravity). These G-conditions are also graphically indicated in Table 6.1.

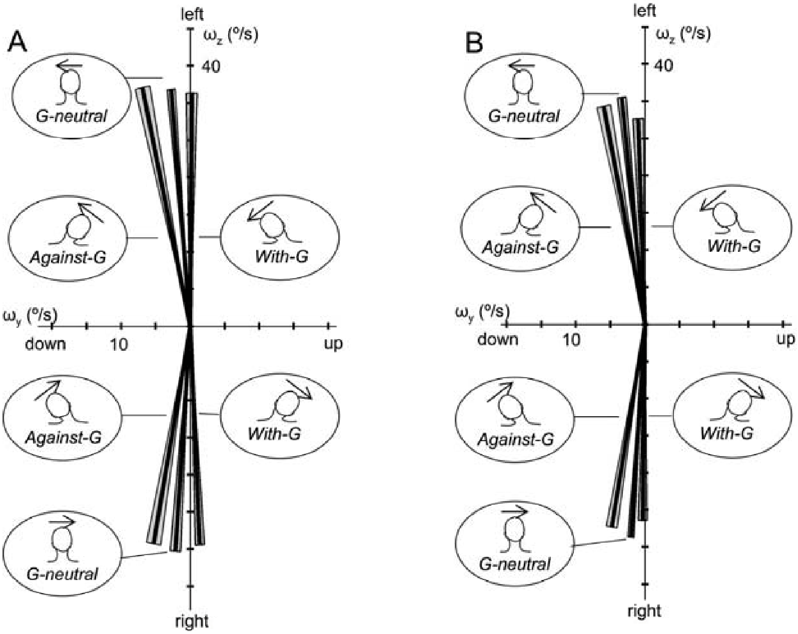


Figure 6.3: Orientation of the eye velocity vector (α in Fig. 6.2) relative to the head-longitudinal axis, for the six experimental conditions. The drawings indicate the corresponding head orientation and direction of the optokinetic stimulus. 'G-neutral' denotes the conditions where the stimulus velocity vector is aligned with gravity, 'With-G' denotes the conditions where the stimulus velocity vector has a downward component relative to gravity (thus requiring an upward eye velocity component to shift the EVV towards gravity), and 'Against-G' denotes the conditions where the stimulus velocity vector has an upward component relative to gravity (thus reguiring a downward eye velocity component to shift the EVV towards gravity). Panel A shows the pretest values of the 3G90 condition, panel B the post-test values. Mean orientation of the EVV (n=12) is indicated by the thick solid line, where its length indicates the mean gain. The gray patches indicate standard error of mean of α.

That head tilt indeed induced significant reorientation of the EVV was confirmed by the statistical analysis: when submitted to a within subjects factorial ANOVA (Centrifuge-condition (4) × measurement condition (6) × test-session (2)), the effect of measurement condition was significant

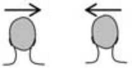
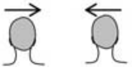
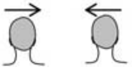
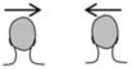
(*F*(5, 50)=33.2, *p*<.0001). A Tukey posthoc test indicated that the two G-neutral conditions, the two With-G conditions and the two Against-G conditions did *not* differ from each other, whereas the head-tilt conditions differed from those with the head erect. The results show that the orientation of the EVV relative to the head yaw axis depended on head tilt and the orientation of the optokinetic stimulus relative to gravity (i.e, Against-G or With-G). In both conditions a significant crosscoupling was induced. Table 6.1 lists the EVV orientation values for the 4 centrifuge conditions, pooled into the G-neutral, With-G and Against-G groups.

Effect of centrifugation on crosscoupling

Figure 6.3B shows the EVV orientation after centrifugation, where changes were found in the orientation of EVV in both With-G conditions: the small upward velocity component changed into a downward velocity component (*F*(5,50)=6.61, *p*<.0001, with Tukey posthoc test). The effect of head tilt on EVV reorientation was analyzed further by calculating the difference in EVV orientation relative to the head-erect condition, thus eliminating the pitch down bias found when the head was erect. The reorientation values for the two With-G and the two Against-G conditions were subsequently submitted to a within subjects factorial ANOVA (Centrifuge-condition (4) × measurement condition (4) × test-session (2)). Here the four measurement conditions indicated the four conditions where the head was tilted. The ANOVA revealed a significant main effect for session (*F*(1, 11)=21.3, *p*=.00075): the head tilt induced reorientation of the EVV was decreased after centrifugation. No differences were found between the four head tilt conditions, indicating that the decrease in reorientation was present in *all* conditions. The mean amount of head tilt induced reorientation (averaged over the four centrifuge conditions and four tilt conditions) equaled 6.5° in the pretest (SD=4.3°, 95% confidence interval = [5.9, 7.1]) versus 5.0° in the posttest (SD=4.0°, 95% confidence interval = [4.5, 5.6]).

TABLE 6.1

Mean EVV orientation (α) and OKN gain, pooled into G-neutral, Against-G and With-G groups.

Centrifuge condition	G-condition		Pretest		Posttest	
			α(º)	OKN gain	α(º)	OKN gain
2G45		G-neutral	5.0 (3.9)	0.85 (0.15)	6.0 (4.0)	0.89 (0.12)
		Against-G	11.6 (7.9)	0.84 (0.19)	11.6 (6.5)	0.87 (0.19)
		With-G	−1.9 (5.6)	0.85 (0.15)	0.7 (6.3)	0.85 (0.15)
2G90		G-neutral	4.6 (3.8)	0.90 (0.14)	5.4 (3.5)	0.87 (0.17)
		Against-G	11.7 (6.5)	0.87 (0.19)	11.1 (6.9)	0.88 (0.19)
		With-G	−1.1 (5.7)	0.85 (0.18)	1.2 (5.1)	0.82 (0.16)
3G45		G-neutral	4.1 (4.8)	0.89 0.13)	4.6 (3.7)	0.89 (0.15)
		Against-G	11.2 (7.7)	0.87 (0.16)	10.7 (6.2)	0.88 (0.17)
		With-G	−1.9 (5.6)	0.82 (0.16)	0.2 (5.1)	0.81 (0.17)
3G90		G-neutral	4.5 (4.3)	0.89 (0.10)	5.2 (3.8)	0.85 (0.19)
		Against-G	11.2 (6.7)	0.89 (0.12)	10.7 (5.9)	0.82 (0.19)
		With-G	−1.5 (4.8)	0.87 (0.11)	1.4 (5.1)	0.77 (0.20)

The ANOVA did not reveal a significant effect of centrifuge condition, indicating that all conditions had a similar effect on EVV reorientation. Inspection of the data revealed that the average decrease of head tilt induced reorientation was largest in the most strenuous condition (3G90, see Figure 6.4), but differences between conditions were small.

Averaged over all observations, mean OKN-gain equaled 0.86 (SD 0.16, see also Table 6.1). Although no differences were found between the pre- and posttest, the tilt-condition (G-neutral, With-G or Against-G) significantly affected OKN gain (*F*(2,22)=16.7, *p*<.001). A post-hoc Tukey test indicated that the gain in the With-G condition was significantly lower than the other two conditions.

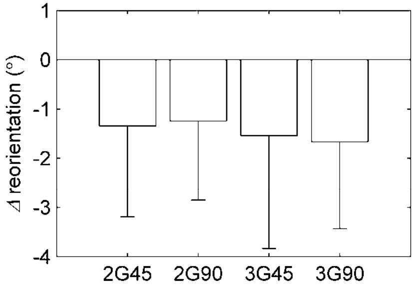


Figure 6.4: Difference in the head tilt induced EVV-reorientation between the pre- and the posttest, for the four centrifuge conditions.

Vector model for OKN

In this section a model is proposed that accounts for the results regarding the orientation of the EVV, both before and after centrifugation. By means of this model, the observed changes in cross-coupling can be related to a decrease in the contribution of VS to the orientation of the EVV.

During optokinetic stimulation, the orientation of the resultant eye velocity vector is determined by the direction of the stimulus and, through VS, by the direction of gravity relative to the head. The current results suggest that there is a third determinant present: regardless of the head orientation, the eye showed a tendency to move down in the head. These three components were combined in a model possibly explaining these observations.

It is proposed that the orientation of the EVV is determined by the sum of the vectors **S**, indicating the stimulus-induced component, **VS** indicating the velocity storage-induced component, and **B** indicating the downward bias. Figure 6.5 depicts the model for the three tilt conditions. **S** is related to the angular velocity of the optokinetic pattern and is always aligned with the head yaw axis, **VS** is hypothesized to be aligned with the Earth-vertical, and **B** is assumed to be aligned with the interaural axis to account for the downward eye motion. The orientation of the EVV (α) then is determined by:

$$\alpha = \arctan\left(\frac{|\mathbf{B}| + |\mathbf{VS}| \cdot \sin(\beta)}{|\mathbf{S}| + |\mathbf{VS}| \cdot \cos(\beta)}\right) \tag{6.1}$$

with β the angle of head tilt.

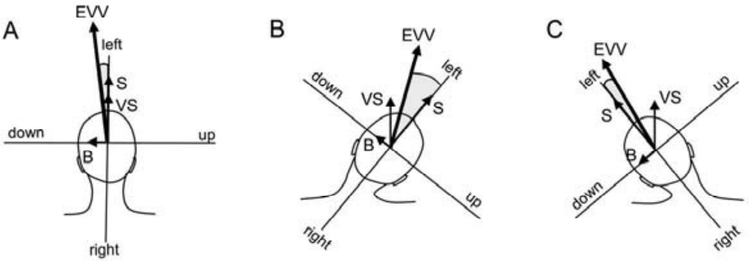


*Figure 6.5: Vector model for OKN, specified for the G-neutral condition (A), the Against-G condition (B) and the With-G condition (C). The stimulus vector **S** is always aligned with the head-longitudinal axis, the velocity storage **VS** vector with gravity, and the bias vector **B** with the inter-aural axis. The sum of these vectors determines the orientation of the resulting EVV (α), indicated by the shaded arcs.*

With the bias-vector included in the model, the different effects of centrifugation in the With-G and the Against-G conditions can be understood. Recall that centrifugation changed the *absolute* orientation of the EVV in the With-G conditions only. For illustration puposes, a complete absence of **VS** is Figure 6.6, depicting a theorectical effect of sustained centrifugation (as is shown later, the actual decrease in VS is obviously less than 100%). When the head is erect, the EVV is shifted further away from the stimulus-axis (Figure 6.6A, compare the orientation of EVV_{pre} with that of EVV_{post}), while it is shifted closer to the stimulus-axis in the Against-G condition (Figure 6.6B). The change in EVV-orientation is largest in the With-G condition, where the EVV shifts to the other side of the ordinate (Figure 6.6C). These changes are qualitatively all in accordance with the experimental data (see Table 6.1 and Figure 6.3).

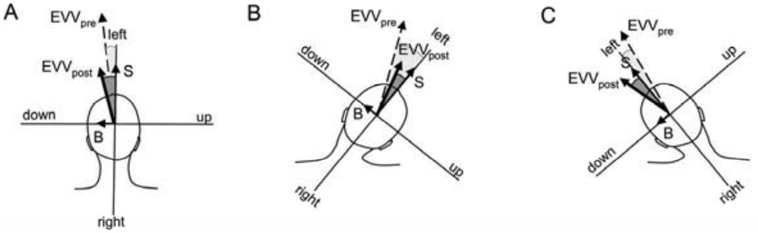


Figure 6.6: Vector model for OKN, specified for the G-neutral condition (A), the Against-G condition (B) and the With-G condition (C). Centrifugation is hypothesized to decrease the effect of velocity storage on the orientation of the EVV. In this example ***VS****=0, leading to changes in the orientation of EVV that are consistent with the data. The orientation of the EVV before centrifugation,* $EVV_{pre,}$ *is indicated by the shaded arc in light-gray whereas the orientation after centrifugation,* EVV_{post} *is indicated in dark gray.*

To analyze this model quantitatively, it was fitted to the data of the most strenuous centrifuge condition (3G90) for each individual subject and assuming variable vector lengths. The length of **S** was set to unity and the relative lengths of **VS** and **B** were determined using Eq. 6.1. The model described the data very well: a comparison of the observed and the predicted values yielded a correlation of r=0.99. The residual sum of squares was 0.06° on average (SD 0.09°). Averaged over all subjects, the lengths of **S** : **VS** : **B** equaled 1 : 0.19 : 0.10 in the prestest (SD_{VS} 0.08; SD_B 0.10) versus 1 : 0.13 : 0.11 in the posttest (SD_{VS} 0.04; SD_B 0.08). This implies a significant reduction in the contribution of VS of 31% after centrifugation ($t(11)=3.19$, $p=.0086$). The change in **B** was not significant.

DISCUSSION

The study described in this chapter focused on the spatial properties of velocity storage (VS) in humans. Because the spatial orientation of the eye velocity vector (EVV) during optokinetic nystagmus is governed by VS-activity (Cohen et al., 1977; Raphan et al., 1979) this parameter was used to determine whether sustained centrifugation affected the VS-mechanism. The results showed that lateral head tilt of 45° induced a reorientation of the EVV of about 6.5° towards the Earth's vertical. This reorientation was independent of the direction of head tilt and was significantly reduced after centrifugation to an amount of 5° on average. However, when the head was erect, a pitch-down bias was observed, already shifting the EVV 5.0° away from the stimulus axis. This caused an asymmetry in the absolute orientation of the EVV relative to the stimulus axis between the conditions where the slow phase was directed against gravity (Against-G, requiring a downward velocity component for alignment with gravity) and where the slow phase was directed in the direction of gravity (With-G, requiring an upward component for alignment with gravity) .

A pitch-down bias and the resulting gravity-dependent asymmetry in EVV orientation have been described before, although the magnitudes of these effects differed per study. Gizzi and colleagues (1994) reported that the EVV was 'closely aligned' with the spatial vertical when the head was erect (mean deviation = 0.5° over 6 subjects, but with a maximum of 9°), and found a large gravity dependence during a 45° head tilt. Relative to the stimulus axis, reorientation of the EVV was 23.5° in their Against-G condition while it was 12.7° in their With-G condition. Moore and colleagues (2005) observed a mean deviation of the EVV of 7.4º (4 subjects) when the head was erect, and an additional 8.9º reorientation due to G_y centrifugation (i.e., tilting the gravito-inertial acceleration 45º to the left and right). These investigators also studied the spatial characteristics of VS during spaceflight, which is discussed below. They suggested that the large magnitude of reorientation as found by Gizzi could be attributed to the contribution of the neck stretch receptors (Mittelstaedt & Glasauer, 1993), because Gizzi used active head tilt as opposed to whole body tilt which was used by Moore c.s.. The current results contradict this hypothesis, because they were obtained using a similar head tilt paradigm. Alternatively, it is possible that the use of electro-oculography, which is known to be prone to crosstalk between horizontal and vertical channels, might have affected their results.

Effect of sustained centrifugation

The most important result of this study was that sustained exposure to hypergravity and the following transition to Earth's gravity led to a reduction of the amount of head-tilt induced reorientation of the EVV. This suggests a decrease in VS-activity, which, when quantified by means of a vector model, was estimated at 31%.

Although this reduction of the reorientation induced by head tilt was present in both the With-G and the Against-G conditions, a significant change in the *absolute* EVV orientation was only found in the With-G condition. This apparent contradiction can be explained by changes in the absolute values for the G-neutral and Against-G conditions. As could be seen in Table 6.1, the angle between the EVV and the head yaw axis increases slightly for the G-neutral conditons where it decreases slightly for the With-G conditions. Although these changes by themselves are too small to become significant, they make that the *difference* between the two vectors (i.e., the reorientation due to head tilt) becomes less after centrifugation.

By incorporating a pitch down bias in the vector model, the experimental results could be replicated very well. This pitch-down bias appeared to be a constant factor in the determination of the EVV-orientation, and both the gravity-dependent asymmetry in EVV-orientation (pretest data), as well as the effects of centrifugation (posttest data) were in accordance with the observed results. It was because of this pitch down bias that a decrease of the VS-vector had a larger effect on the absolute EVV orientation in the With-G conditions than in the Against-G conditions (see Figure 6.6). In addition, the changes in the EVV orientation in the G-neutral condition (head erect) were also in accordance with the data.

This suggests that the EVV-orientation is determined by 1) the direction of the stimulus (which was, in this case, always head-fixed), 2) the direction of gravity relative to the head (Earth-fixed), and 3) the pitch-down bias. Taking the latter component head-fixed as opposed to Earth-fixed yielded a significantly smaller sum of residuals in the data fits ($t(23)=2.41$, $p<0.05$), thus suggesting a head-fixed bias as has been used in the current analyses. It remains unclear whether this bias has a functional meaning or results, for example, from a kinematic constraint. The head-fixed nature of this behaviour, together with the observation that this pitch down bias is also present during vertical axis rotation in humans (Haslwanter et al., 1996), appears to favour the latter explanation. An exact answer is, however, still lacking.

It should be stressed that the model only estimates the *orientation* of the EVV and not its magnitude. The OKN gain was affected by head tilt, as it was smallest in the With-G conditions (i.e., horizontal slow phase eye velocity has a downward component relative to gravity). Such a gravity-dependent difference in horizontal OKN-gain has been observed before (Kitama et al., 2004; Lafortune et al., 1991) and is also present in vertical OKN. With the head erect, slow phase velocity is usually greater during an upward stimulus than during a downward stimulus, although this asymmetry is larger in monkeys than in humans (e.g., Matsuo & Cohen, 1984; Ogino et al., 1996; Van den Berg & Collewijn, 1988). Nevertheless, this suggests that gravity has an effect on OKN-gain, whereas velocity storage predominantly affects the spatial properties of OKN.

As mentioned before, sustained centrifugation is also known to affect the temporal properties of VS. Groen (1997) found a reduction of the horizontal aVOR time constant after exposure to a $3G_x$ load for 60 min. Such temporal effects should then also be present in the optokinetic afternystagmus (OKAN), which is the prolongation of nystagmus when the visual stimulus is switched off (Cohen et al., 1977; 1981; Raphan et al., 1979). However, inspection of the current data revealed that we were not able to induce a reliable and robust OKAN response in all subjects. Responses generally were short and variable. This might be due to the fact that we used a flat projection screen with a limited field of view instead of a rotating drum with an unlimited field of view. Nevertheless, we analyzed the available OKAN-data of the G-neutral condition and found a small reduction of the VS-time constant[9]. Although this reduction is in accordance with the results of Groen (1997), and with the hypothesized reduction in VS-activity, a more compelling stimulus is necessary to substantiate these results.

Does spaceflight also lead to changes in velocity storage characteristics? A reduction of the dominant aVOR time constant have been observed, although the results varied between astronauts (Oman & Weigl, 1989; Oman & Balkwill, 1993; Oman et al., 1996). Moore and colleagues (2005) investigated the spatial orientation of optokinetic nystagmus during G_y centrifugation in four astronauts during the Neurolab mission, but observed no significant changes in EVV reorientation during or after the flight. It was concluded that the EVV

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[9] To that end, horizontal OKAN slow phase velocity (SPV) was fitted by a double exponential curve ($SPV=A_1 \cdot e^{-t/\tau 1} + A_2 \cdot e^{-t/\tau 2}$, see Jell et al., 1984). The first and smallest time constant accounts for the rapid decay in SPV at the end of stimulation, whereas the longer time constant is associated with VS-activity. Averaged over the available data, this latter time constant equaled 9.1s (SD 8.9) in the pretest and 6.5s (SD 5.9) in the posttest.

reorientation depended on the magnitude of the interaural stimulation, which was similar before, during, and after the flight. A post flight decrease in the spatial characteristics of velocity storage was, on the other hand, observed in 2 monkeys (Dai et al., 1998). The small amount of astronauts tested during the Neurolab mission might have contributed to the lack of space flight effects. The data of the current study show that responses do vary between subjects, and changes are relatively small.

Velocity storage is a central, i.e., merely neural mechanism (Raphan et al., 1979). The fact that the hypergravity load was applied in the fore-aft direction (i.e., G_x-load) whereas we measured an effect in the plane orthogonal to this direction (i.e., the roll plane) illustrates that adaptation to a novel gravitational environment is a central process too. Possibly, the effects on VS would have been larger when the G-load would have been applied along the interaural axis (i.e., G_y, parallel to the roll plane), by having the subject lying on their side in the gondola. Alternatively, G_x stimulation during centrifugation could have been combined with OKN recordings during pitch body tilt, inducing a reorientation of the EVV in the sagittal plane (crosscoupling from horizontal to torsional eye movements).

Is VS-activity related to spatial orientation?

In the remaining part of this chapter we will return to the tilt/translation ambiguity and discuss how a reduction of VS-activity may relate to spatial disorientation as experienced after sustained centrifugation. As mentioned in the introduction, many models for spatial orientation are based on the idea that the brain uses information about angular velocity to discriminate translation from tilt (e.g., Angelaki et al., 1999; Bos & Bles, 2002; Merfeld et al., 1993; Merfeld et al., 1999; Zupan et al., 2002). Although the models may differ in detail, they are all based on similar equations that incorporate the interaction between otolith and semicircular canal signals in order to obtain an estimate of gravity (see also Chapter 1, Eq. 1.2). Investigation of neural activity of motion sensitive neurons in monkeys showed that the observed neural firing rates could well be described by these equations of motion, suggesting that these equations are indeed used by the brain (Angelaki et al., 2004; Green et al., 2005; Shaikh et al., 2004; Yakusheva et al., 2007)[10]. An important aspect of this strategy to solve the tilt/translation ambiguity is that it requires a *temporal integration of angular velocity information*. Green and Angelaki (2003, 2004) suggested that this integration could well be performed by the VS-integrator. By recording the eye movements of monkeys during combined tilt and translational movements, they showed that these integrated angular velocity signals were necessary to generate the appropriate ocular responses (i.e., ocular counter roll and/or linear VOR). The behaviour classically attributed to the VS-integrator (like improving the low frequency behaviour of the VOR) can then be seen as a by-product of this integrative action rather than as its main purpose.

Although evidence for the role of the VS integrator in spatial orientation remains to be substantiated both theoretically and experimentally, it is a promising hypothesis because it links a number of findings regarding adaptation to a new gravitational environment. First of all, the symptoms that are usually observed after sustained centrifugation all relate to a disturbed spatial orientation. Subjects show a deteriorated postural stability (Bles & De Graaf, 1993), and experience all kinds of motion illusions, suggesting a disturbed sense of self motion. As a result, they also suffer from motion sickness, which is closely related to spatial disorientation (Bles et al., 1998a, see also Chapter 1).

Second, a disturbed canal-otolith interaction has earlier been suggested as a contributor to the centrifugation induced effects (Bles & De Graaf, 1993; Bles et al., 1997). This is illustrated by the finding that motion sickness is especially provoked by head movements that tilt the head with respect to gravity (i.e., pitch and roll when erect, Bles & De

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[10] These studies used a slightly different version of Eq. 1.2, that was suitable for the frequency domain of the semicircular canals: $\frac{d\mathbf{g}}{dt} = -\boldsymbol{\omega} \times \mathbf{g}$

Graaf, 1993; see also Chapter 2), and not by head movements without a tilt component. Importantly, static or slow tilt (<0.1 Hz) is not provocative, which is also outside the frequency range where the semicircular canals contribute to resolving the tilt/translation ambiguity (Angelaki et al., 1999).

Third, a disturbed ability to discriminate tilt from translation has recently been recognized as a factor contributing to disorientation experienced by astronauts returning to Earth (Merfeld, 2003). Merfeld suggested that "the functional role played by the neural networks that perform the calculations (i.e., to solve the tilt/translation ambiguity) will deteriorate in the absence of a gravitational field". Although this is a perfectly functional adaptation to the microgravity environment, it obviously leads to an inadequate spatial orientation perception when back on Earth. Accordingly, it has been shown that the ability to control dynamic roll tilt (i.e., keep yourself upright while exposed to pseudo-random motion in roll) was deteriorated in astronauts after spaceflight, while the ability to counteract *static* roll was unchanged (Merfeld, 1996). This again stresses the importance of dynamic rotational cues in solving the tilt/translation ambiguity in movements within the mid-frequency range.

Conclusion

Taken all together, the arguments presented above suggest that the spatial disorientation occurring after sustained centrifugation and possibly also after space flight are, at least in part, associated with a deteriorated ability to discriminate translation from tilt. The results of the present study add to the data showing that the gravity transitions mentioned above also affect the VS-mechanism. Linking the VS-integrator directly to spatial orientation would be an important next step in understanding the cause of the disorientation after both gravity transitions. As suggested by Green & Angelaki (2004), further evidence for such a link can be obtained by studying how modifications in VS-activity, associated with lesions in the associated brain areas like the nodulus/uvula or the vestibular commissural pathways (e.g. Angelaki & Hess, 1995; 1998; Katz et al., 1991; Wearne et al., 1997) affect the ability to discriminate tilt from translation.