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Validation of centrifugation as a countermeasure for otolith deconditioning during spaceflight: Preliminary data of the ESA SPIN study[1]

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Abstract. In the framework of further space exploration, countermeasures to combat the drawbacks of human space flights are essential. The present study focuses on the influence of microgravity on the otolith-ocular reflex and aims to test the hypothesis of artificial gravity being an adequate countermeasure for the deconditioning of the aforementioned reflex. The so-called SPIN study, commissioned by the European Space Agency, can be considered as a control experiment in the broad sense for the Neurolab mission (STS-90) during which 4 crewmembers of the space shuttle were subjected to in-flight centrifugation on the visual and vestibular investigation system (VVIS). After their nearly 16-day mission, they did not suffer from orthostatic intolerance and spatial disorientation. In addition, the relevant parameters of the otolith-ocular interaction remained unaffected. For this study cosmonauts from a long duration stay in the International Space Station that were not centrifuged in-flight were tested on the VVIS (1 g centripetal interaural acceleration) on 6 different days. Three measurements were taken about 1.5–2 months prior to launch and 3 were taken at 1, 4 and 9 days after return from space. Ocular counter-rolling was measured before, during and after rotation on the VVIS using infrared video goggles and compared pair wise using Friedman tests. The perception of verticality was monitored using an ultrasound system for perceptual evaluation. The preliminary results of 4 cosmonauts showed a surprisingly large inter-individual variability of the measurements. Although OCR and perception of verticality appeared to be influenced overall by the exposure to microgravity, the wide variability among the cosmonauts obscured any statistical significance, in particular due to one cosmonauts being inconsistent with the other 3. Despite the specificity of the tests under normal conditions, the diverse response to spaceflight of our subjects exposes the complexity of the peripheral and central neural adaptive processes.

Keywords: Otolith-ocular interaction, artificial gravity, VVIS, space motion sickness

1. Introduction

Since the earliest manned flights, researchers have taken a great interest in altered gravitational environments. The challenging conditions that are inherent to some of those environments not only require technological innovations, but they provide the ideal setting to study the adaptability and plasticity of the human body

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and brain. However, understanding how the human body responds to microgravity exposure has proven difficult. Due to the 'lack' of Earth's gravity in space, different processes in the human body are disorganized. Up to 60% of all astronauts and cosmonauts suffer from space motion sickness (SMS) and spatial disorientation during the first days in space [1–4]. Apart from that, bone decalcification, muscular atrophy and the deconditioning of the otolith-ocular and vestibulo-sympathetic reflexes are major disadvantages during and after a (long) stay in microgravity. The issues that astronauts have to cope with are often similar to those encountered by (vestibular) patients. From that point of view, not only the astronauts and cosmonauts, but those patients also can benefit from space research.

On return from space the astronaut's body has to readapt to a 1 g-environment. The first few days after their return from space, a large percentage of all astronauts and cosmonauts (about 64%, [5,6]) suffer from orthostatic intolerance and spatial disorientation. The otoliths not only have a key role in the latter, several studies have shown that the otoliths also play an important role in the activation of the sympathetic outflow in response to postural changes [7–11]. That activation triggers the vestibulo-sympathetic reflex that is responsible for the preservation of the blood flow to the brain during orthostatic stress by changing the heart rate and vascular tone. Deconditioning of the otoliths can therefore lead to the aforementioned orthostatic intolerance.

In the framework of further space exploration, countermeasures to combat the drawbacks of human space flights are essential. The here described study focuses on the influence of microgravity on the otolith-ocular reflex and aims to test the proposition of the use of artificial gravity as an adequate countermeasure for the deconditioning of the otolith-ocular and the vestibulo-sympathetic reflex. This so-called SPIN study (Validation of centrifugation as a countermeasure for otolith deconditioning during space flight), was originally commissioned by NASA as a pre/post shuttle control study for the Neurolab centrifugation experiment (Principal Investigator S. Moore) flown in 1998, but due to limited availability of shuttle missions post-STS 107 the study was implemented by ESA as a pre/post ISS mission study (F. Wuyts PI, S. Moore and G Clement co-PI). During the Neurolab mission, four crewmembers of the space shuttle (STS-90) were subjected to in-flight centrifugation on a specially designed rotatory chair, the visual and vestibular investigation system (VVIS). After their nearly 16-day mission, those 4 astronauts did not suffer from orthostatic intolerance and spatial disorientation [12]. That was remarkable since – as mentioned before – up to 64% of all astronauts that were not exposed to in-flight centrifugation suffer from orthostatic intolerance and spatial disorientation. In addition, the relevant parameters of the otolith-ocular interaction remained unaffected [12–14]. To validate the hypothesis that states that in-flight centrifugation can serve as a countermeasure for the deconditioning of the otolith-ocular and vestibulo-sympathetic interaction, the SPIN study aims to assess the otolith-ocular interaction and the vestibulo-sympathetic reflex in 6 cosmonauts that were not exposed to in-flight centrifugation. They were subjected to different test sessions on the VVIS and multiple passive tilt tests prior to and after a 6-month stay in the International Space Station. This article describes the preliminary results of the SPIN study in four cosmonauts.

2. Subjects and methods

2.1. Study design

Each experimental session consisted of two tests. First the cosmonauts were rotated on the VVIS, described in the next paragraph, while the ocular counterrolling (OCR) of both eyes was measured using three-dimensional infrared video oculography. In addition, the cosmonaut's perception of verticality was monitored using an ultrasound system for perceptual evaluation. For that purpose, the cosmonaut was asked to keep a joystick upright (along the gravitational vector) throughout the entire experiment as if there was a tray on top of the joystick that had to be kept horizontal (according to the cosmonaut's perception). We intentionally chose this nonvisual, somatosensory measure of roll-tilt perception since visual estimates such as the subjective visual vertical or horizontal are confounded by an offset due to the OCR that simultaneously occurs [15,16]. Three different moments were selected: a 10 s baseline prior to the rotation, a 10 s period about 40 s after the maximal velocity was reached, and a 10 s period after the stop of the VVIS. During the rotation, the gain was defined as the indicated angle divided by the tilt angle of the gravito-inertial acceleration (GIA) vector at the head centre. Prior to the rotation, the ultrasound system was 'calibrated' by asking the subject to indicate specific angles (upright, 15°, 30° and 45° to the left and the right; 15° and 30° forward and backward). Linear regression was used to determine the correspondence between the indicated angles and the 'theoretical', predetermined angles.

After the centrifugation test, the cosmonauts were subjected to a passive tilt test to investigate the vestibulo-sympathetic reflex. Since this article focuses on the impact of microgravity on the otolith-ocular reflex, the results of that test are not discussed here.

Each test was scheduled on six different days: 3 sessions were held approximately 1.5–2 months prior to the launch to determine baseline ('unstressed') conditions (baseline data collection, BDC). The remaining 3 sessions were held immediately after the cosmonaut's return from space on R+1, R+4 and R+9 (with R = day of return from space). All sessions were done at the Gagarin Cosmonaut Training Centre (GCTC) in Star City (Moscow, Russia). For the SPIN study, the cosmonauts were not centrifuged in-flight. The study was approved by the Institutional Review Board of the ESA and the Antwerp University Hospital and all cosmonauts gave a written informed consent.

2.2. *The visual and vestibular investigation system (VVIS)*

The VVIS, depicted in Fig. 1, is the original centrifuge that was used during the Neurolab mission, and for the purpose of the SPIN study placed in a lab in GCTC in Star City. It is mini centrifuge that allows Earth vertical rotation. Although a configuration where the subject is lying on the back was also used during the Neurolab mission, we only used the configuration where the cosmonaut is in an upright sitting position. In the upright position, a fixed distance of 0.5 m between the axis of rotation and the subject's head centre was present. The orientation of the seat – left-ear-out (LEO) or right-ear-out (REO) – and the direction of the rotation – clockwise (CW) or counterclockwise (CCW) – could be chosen, but due to the nauseating sensations during a 'back to motion'-configuration reported during the Neurolab mission (unpublished results), the direction of the rotation was adapted to the orientation of the seat so that the subject always faced the motion (CW rotation in LEO-configuration and CCW rotation in REO-configuration). After a calibration of the video goggles and a recording of a baseline, the cosmonaut was accelerated CCW in a REO set up at a rate of $30°/s^2$ up to an angular velocity of 254°/s. That velocity was chosen to obtain a centripetal acceleration of 1 g and a concomitant tilt of the GIA vector of 45° at the level of the head centre. After the acceleration phase, a steady state phase was built in to allow

Fig. 1. The visual and vestibular investigation system is a mini centrifuge that allows Earth vertical rotation. A fixed distance of 50 cm between the axis of rotation and the head centre is present. The right-ear-out-configuration is depicted.

the cupula of the (horizontal) semicircular canals to return to its original position. A fixation LED was shown on the monitor in front of the cosmonaut's head, to determine the level of OCR. The level of OCR was determined again just before the deceleration of the VVIS ($-3°/s^2$). Forty seconds after the chair had come to a complete stop, the level of OCR was determined a last time. The orientation of the rotation chair was then changed to the LEO-configuration and CW rotation, and the same protocol was repeated.

During the rotation, the heart and respiration rate were carefully monitored using a wireless online electrocardiogram and a LifeShirt monitoring system (VivoMetrics Inc, Los Angeles, CA, USA). The analysis of those data however was beyond the scope of this study.

2.3. *Subjects*

Results of the VVIS experiments are based on the data obtained from 4 male cosmonauts. However, not all sessions were completed in each subject. Due to medical issues, the crew surgeon did not allow the second cosmonaut to participate in the R+1 and R+4 measurements. The third subject only completed the REO-rotation on the second day after his return from space. The scheduled measurements on R+1 and R+9 were delayed one day in the fourth cosmonaut due to

Table 1
Overview of the cosmonauts (Cosmo) that participated in the SPIN study and the test sessions that they completed. # days in μG = number of days in microgravity; BDC = baseline data collection; L-X = launch minus X days; R = day of return from space; LEO = left-ear-out-configuration

Cosmo	Age [year]	# days in μG	BDC 1	BDC 2	BDC 3	R+1	R+4	R+9
1	46	192	L-60	L-56	L-51	+	+	+
2	44	199	L-69	L-67	L-63	–	–	+
3	35	199	L-68	L-64	L-62	R+2, no LEO	+	+
4	48	188	L-54	L-50	L-47	R+2	+	R+10

organizational reasons. Table 1 provides an overview of the different cosmonauts and the sessions they completed.

2.4. Statistical analysis

Given the low number of cosmonauts, it could be expected that the statistical power was too low for a full statistical analysis. For completeness, a non-parametric approach was nevertheless used to investigate possible effects of the prolonged stay in microgravity. Absence of significance in this study is surely not equivalent to the absence of effects.

Since three sets of data were collected about one month and a half to two months prior to the launch, those baseline data sets were compared pair wise using a Friedman test. If no differences were present, the results of those 3 measurements were averaged. Afterwards the pre-flight values were compared to the post-flight data sets using Friedman tests as well. The results of the REO and LEO-configuration were compared pair wise using Wilcoxon matched-pairs signed-ranks tests. Similar tests were used to investigate possible differences between the OCR of the left and the right eye.

Statistical analysis was performed using PASW Statistics 18.0 (SPSS Software®, SPSS Inc, Chicago, IL, USA) and the significance level was set at 5%.

3. Results

3.1. Ocular counter-rolling

Comparison of the three baseline data sets using Friedman tests showed no differences in all cosmonauts, so for each cosmonaut the results of those baseline measurements were averaged. Figure 2 shows the binocular results for both runs at the three moments from which the OCR was determined. Prior to each acceleration, 2 baseline data sets were collected, but since they did not differ significantly from each other or from zero (Wilcoxon matched-pairs signed-ranks test, $p > 0.05$) they were omitted in the figures.

Figure 2 shows the large variability of the measured ocular counter-rolling among the 4 cosmonauts. In the REO-configuration, the R+2 and R+4 OCR values that were recorded just prior to the deceleration were consistently lower than the BDC value (except in the left eye of the fourth cosmonaut). In the LEO-configuration, the second rotation of each session, that consistency was gone. The statistical tests however were unable to confirm the differences between the pre- and post-flight measurements (Friedman test, $p > 0.05$), nor could they indicate any differences between the left and right eye (Wilcoxon matched-pairs signed-ranks test, $p > 0.05$). Although the OCR appeared to evolve during the rotation (most of the times the OCR decayed, although in some sessions the OCR increased), those differences were not significant (Wilcoxon matched-pairs signed-ranks test, $p > 0.05$). In addition, a Wilcoxon matched-pairs signed-ranks test indicated that those differences were identical in the REO and LEO- configuration ($p > 0.05$). In both configurations (REO and LEO) and in each session, the OCR had returned to the baseline (zero) value when the OCR was determined about 40 s after the VVIS had come to a complete stop (Wilcoxon matched-pairs signed-ranks test, $p > 0.05$). At the right side of each graph is the mean OCR depicted of the 4 crew members of the Neurolab mission at R+1 [14]. Comparing these post flight data with results obtained in the current 4 cosmonauts who were not exposed to in-flight centrifugation, one can see that the Neurolab post flight data correspond best with our pre flight OCR data.

3.2. Subjective perception

Similar to the OCR, the perception of verticality did not change significantly during the three BDC sets (Friedman test, $p > 0.05$), so the results of the three BDCs were averaged. The calibration of the ultrasound system indicated that all 4 cosmonauts could estimate the predetermined angles relatively accurately during the BDCs as illustrated by the slopes of the linear regression in Table 2 that approximated one. A slope that

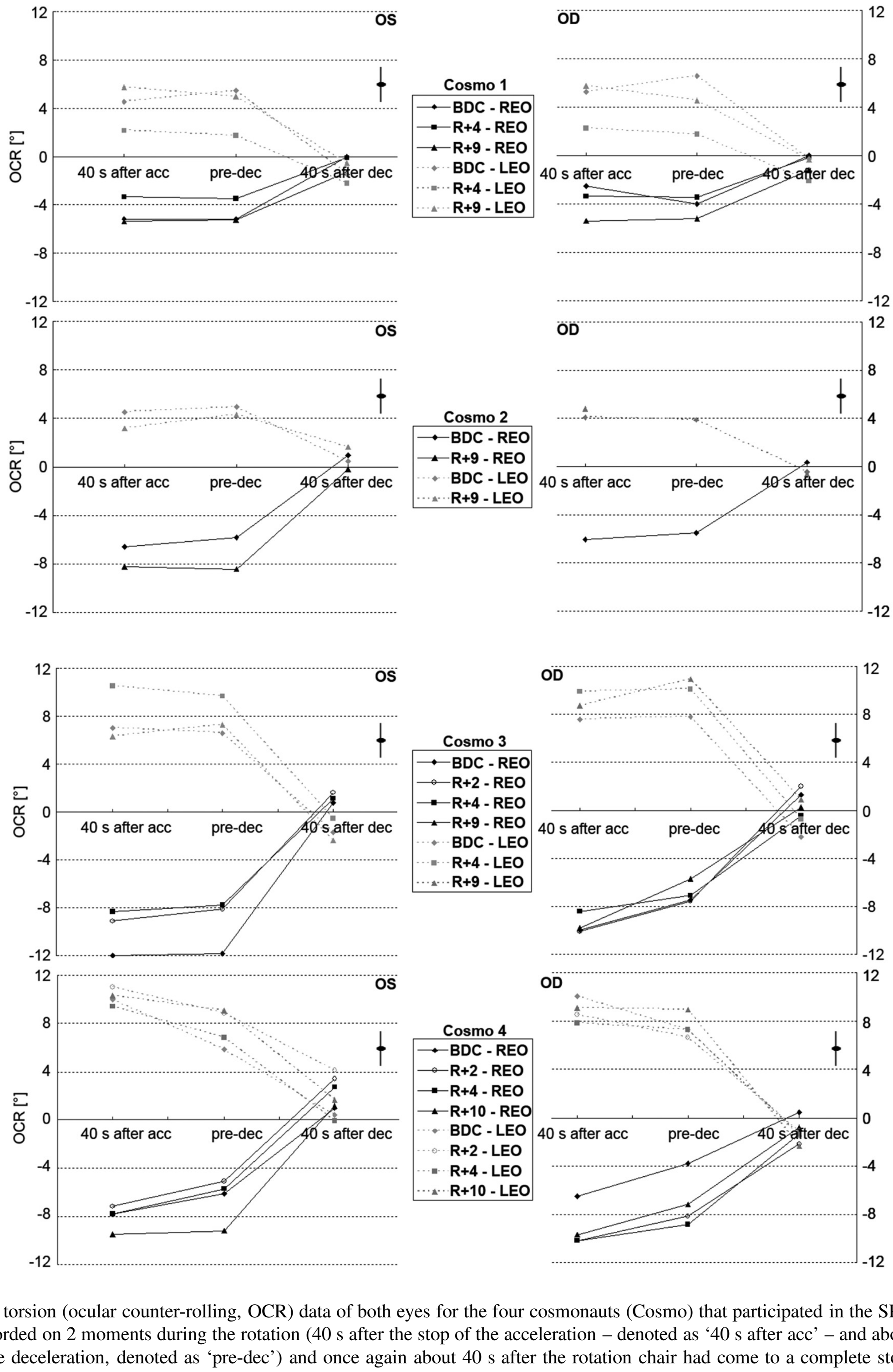

Fig. 2. Ocular torsion (ocular counter-rolling, OCR) data of both eyes for the four cosmonauts (Cosmo) that participated in the SPIN study. The OCR was recorded on 2 moments during the rotation (40 s after the stop of the acceleration – denoted as '40 s after acc' – and about 10 s before the start of the deceleration, denoted as 'pre-dec') and once again about 40 s after the rotation chair had come to a complete stop (denoted as '40 s after dec'). At the right of each graph is the mean ± SD OCR depicted of the Neurolab measurement on R+1 of the 4 crew members (5.9 ± 1.4 deg, [14]). BDC = baseline data collection; R = day of return from space; REO = right-ear-out (configuration); LEO = left-ear-out (configuration); OD = oculus dexter (right eye); OS = oculus sinister (left eye).

Table 2
Calibration slopes of the four cosmonauts that were tested on 6 different moments. The results of the three baseline data sets (baseline data collection, BDC) were averaged since they did not differ significantly. When the slope is smaller than 1, the cosmonaut underestimated the predetermined angles. In case of a slope larger than 1, an overestimation of the predetermined angles occurred

Cosmonaut	BDC	R+1/R+2	R+4	R+9/R+10
1	0.94	0.84	0.81	0.98
2	0.87	–	–	0.67
3	0.92	0.79	0.63	0.48
4	0.97	1.01	1.18	1.14

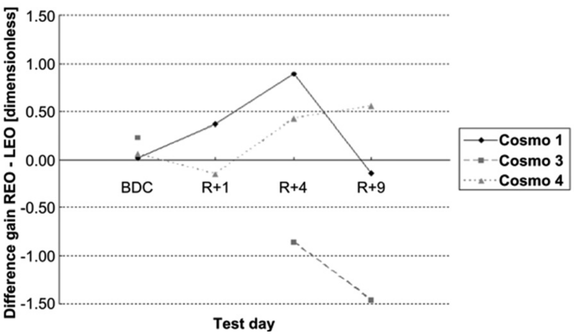

Fig. 3. Differences in subjective perception gain of the right-ear-out (REO) and left-ear-out (LEO)-configuration recorded during the different test sessions. BDC = baseline data collection; R = day of return from space.

was smaller than 1 resulted from the fact that the indicated angles were smaller than the predefined, 'theoretical' angles, whereas a slope larger than 1 indicated an overestimation of the theoretical angles.

Although the post-flight evolution of the slope of the calibration was clearly different in the 4 cosmonauts (decrease of the slope in cosmonauts 1 and 3 on R+1/R+2 and R+4, increase in cosmonaut 4), the Friedman test was unable to confirm those differences ($p > 0.05$).

When the pre-flight indicated angle of tilt during and after the rotation were compared to the post-flight data, the Friedman tests indicated no statistically significant differences ($p > 0.05$). Nevertheless, when the evolution of an individual cosmonaut was investigated, clear differences were present. During the BDCs the third cosmonaut overestimated the GIA tilt, whereas the remaining 3 underestimated the subjective tilt. That perception appeared to change entirely post-flight, even though exactly the same instructions were given. For example, on the second day after his return (R+2), the third cosmonaut did not indicate any tilt during the REO-rotation.

In each session, the cosmonaut's perceived angle of tilt returned to the baseline (zero) value 40 s after the rotation had come to a stop (Wilcoxon matched-pairs signed-ranks test, $p > 0.05$).

No statistically significant differences between the REO and LEO-configuration were found on any test day (Wilcoxon matched-pairs signed-ranks test, $p > 0.05$) in the 4 cosmonauts, although clear differences could be noted when the individual cases were studied (Fig. 3). Especially post-flight the REO-LEO differences appeared to become more distinct.

4. Discussion

Deconditioning of the otolith-ocular and vestibulospinal reflex following adaptation to microgravity has been proposed to be a key factor in the gaze control, locomotor and postural problems in astronauts and cosmonauts on return to Earth [13,17–24]. Ocular counterrolling has therefore often been used as indicator for the effect of microgravity on the otolith system. Previous studies in altered gravitational settings such as the microgravitational environment in space or during parabolic flights have shown that such altered environment significantly affects the torsional position of both eyes [25–27]. About 75% of the astronauts and cosmonauts that were not exposed to in-flight centrifugation showed a decreased OCR post-flight, even after short-duration missions [13,14,26,28]. In this study, the 3 cosmonauts from a long-duration mission that could be tested on all post-flight sessions all showed a decreased OCR during the first rotation (REO, CCW rotation) of the R+1/R+2 and R+4 measurement. This decrease has been attributed to the absence of the gravity-dependent dynamic stimulation of the otoliths [29] and has been found to persist for several days on return to Earth [13,22,29–31]. Apart from the otolithic contribution to the OCR, evidence for an extraotolithic contribution of the somatosensory system and graviceptors has been found in human and animals [32,33]. The disorder of those systems due to the absence of gravity in space can also account for the decreased OCR. The astronauts that were centrifuged in-flight during the Neurolab mission, did not display such a decrease in OCR, indicating that the exposure to intermittent periods of artificial gravity had prevented the deconditioning of the otolith-ocular reflex [13]. Whereas the more traditional countermeasures (exercise, lower-body negative pressure devices or resistive garment) try to alleviate the symptoms of the deconditioning, artificial gravity attempts to remove its cause [34]. During the second rotation of each session

(LEO, CW rotation), the consistency in OCR decrease however disappeared due to unclear reasons. It seems unlikely that an inter-individually variable training effect occurs within one session, but that the effect has disappeared at the start of the next session. Further research is thus needed to explain that divergence.

Although the recovery process is known to vary widely in intensity and duration among cosmonauts, the OCR values of the investigated cosmonauts had almost returned to the baseline conditions on the last post-flight measurement (R+9/R+10).

Apart from the overall post-flight decrease in OCR, it could be noted that the altered gravitational state appeared to have affected both eyes independently, causing disconjugate eye movements. The disconjugacy score, reflecting the difference between both eyes, has been proposed to be an indicator of space motion sickness [27,35–37]. Retrospective studies showed that astronauts or cosmonauts who suffered from space motion sickness had a significantly higher disconjugacy score than those who did not suffer from SMS. The considerable inter-individual variability has been documented in several studies [25–27] and has been found to be consistent with the otolith asymmetry hypothesis. That hypothesis was first proposed by von Baumgarten and Thümler [38] who stated that a functional asymmetry between the left and right utricles might exist due to differences in size and/or weight. They hypothesized that the asymmetry is well compensated in the normal Earth's gravitational environment, but in altered gravitational conditions where the central compensation is inadequate, the asymmetry gets unmasked. Although no disconjugacy scores were calculated in this study, considerable differences between both eyes were present, even pre-flight. However, statistical power was too low to confirm those differences.

In a separate part of the SPIN study, the SPIN-D study (Validation of a specific drug against g-level transition induced spatial disorientation and orthostatic intolerance), we investigated the influence of different drugs on the vestibular and cardiovascular system in healthy controls. There we found that the combination of promethazine and dextro-amphetamine significantly affected the level of utricular asymmetry [39]. Since promethazine has been proven to be relatively efficient for the treatment of SMS, those findings corroborated the hypothesis of otolith asymmetry playing an important role in evoking SMS. In this study we did not use the unilateral centrifugation test for the unilateral assessment of both utricles, so no conclusions on the level of utricular asymmetry can be made. Recent work by Nooij et al. [40] however suggests that the utricular asymmetry is not the only contributing factor, but that the canal system might be involved in generating SMS as well.

A combination of intermittent exposure to artificial gravity and pharmacological countermeasures therefore might provide a solution to the problems that are inherent to an exposure to microgravity.

The OCR changes – although not significant – that occurred during the rotation can be attributed to the contribution of the semicircular canals. As demonstrated by Buytaert et al. [41], the (horizontal) semicircular canals evoke an ocular torsion that decays exponentially as soon as the acceleration becomes zero again. The time constant of this decay shows a large inter-individual variability as illustrated by Buytaert et al. [41], and that variability largely accounts for the differences between the 4 cosmonauts seen during the rotation.

Aside from the changes in OCR, the subjective perception of verticality was also affected by the long-duration exposure to microgravity. Whereas OCR is mainly a reflex response generated by the shearing (centrifugal) force acting on the utricular maculae (at the peripheral level), the perceived tilt is a combination of multisensory integration presumably related to higher cognitive levels [42]. During the rotation the cosmonaut perceives the GIA as the vertical and therefore feels tilted in the roll plane. This is called the somatogravic illusion [43]. Consequently, to compensate for the tilt of the GIA and keep the joystick with the imaginary tray 'upright', the cosmonaut will rotate the joystick in the opposite direction. Whereas normal subjects tend to overestimate the roll angle [42], three of the four tested cosmonauts in this study were able to adequately indicate the predetermined angles during the calibration of the pre-flight sessions (slope of the calibration regression curves approaching one). Their experience as (jet) pilot might account for this accuracy. During the rotation however they all slightly underestimated the roll angle. While we recorded a decreased level of roll tilt on R+1/R+2, Clément et al. [44] found an increase in subjective tilt perception on return to Earth. They attributed the change in tilt perception to a central adaptation process due to the prolonged exposure to weightlessness. In particular, they presumed that the overestimation of tilt in the returning astronauts was the result of a reduction in the amplitude of their idiotropic vector (the internal bias signal that is aligned with the upward head axis; [45]).

After the deceleration, all cosmonauts quickly indicated that they had returned to the 'real' upright position (corresponding to the gravitational vector), even post-flight. These findings corresponded to those of Clément and Deguine [42] and Clément et al. [44].

5. Conclusion

The preliminary results of 4 cosmonauts already showed a large variability in responses after a long duration stay in microgravity. Nevertheless, during the post-flight measurements (R+1/R+2 and R+4) a tendency for decrease in OCR could be noted which was not present in the astronauts that were exposed to in-flight centrifugation during the Neurolab mission. These findings suggest that in-flight centrifugation indeed acted as countermeasure for otolith-deconditioning. In this phase of the study however, the statistical power was too low to confirm any pre- and post-flight differences. We therefore expect that the full extent of the influence of centrifugation during microgravity will become clear when the remaining cosmonauts will be tested and a ground-based control study will be performed. Thus validation of the Neurolab findings awaits further investigations.

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