Decreased otolith-mediated vestibular response in 25 astronauts induced by long duration spaceflight

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Running head/short title: Decreased OCR response following spaceflight

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artificial gravity

Abstract: The information coming from the vestibular otolith organs is important for the brain when reflexively making appropriate visual and spinal corrections to maintain balance. Symptoms related to failed balance control and navigation are
commonly observed in astronauts returning from space. To investigate the effect of microgravity exposure on the otoliths, we studied the otolith-mediated responses elicited by centrifugation in a group of 25 astronauts before and after 6 months of spaceflight. Ocular Counter-Rolling (OCR) is an otolith-driven reflex which is sensitive to head tilt with regard to gravity and tilts of the gravito-inertial acceleration vector during centrifugation. When comparing pre- and postflight OCR, we found a statistically significant decrease of the OCR response upon return. Nine days after return, the OCR was back at preflight level, indicating a full recovery. Our large study sample allows for more general physiological conclusions about the effect of prolonged microgravity on the otolith system. A deconditioned otolith system is thought to be the cause of several of the drawbacks seen in returning astronauts, such as spatial disorientation and orthostatic intolerance. This knowledge should be taken into for future long-term space missions.

New & Noteworthy: Long-duration spaceflight causes a significant decrease in otolith-mediated response OCR

Introduction

To coordinate movements, ensure balance and maintain stable gaze, humans depend on the peripheral vestibular labyrinth, located bilaterally in the inner ear. The vestibular system senses head movements and provides the brain with the necessary information about our spatial orientation. The vestibular system consists of two main parts; the semicircular canals (SCC), which sense rotational movements and the otolith organs detecting the sum of linear accelerations acting on the head. The sum is referred to as the gravito-inertial acceleration (GIA) vector (see figure 1).
Otolith-driven eye movements reflect the response of the sensory epithelia to both translation and tilt (with respect to gravity) of the head. One example of an otolith-driven response is ocular counter-rolling (OCR), which is generated when we turn around a corner (Imai et al., 2001) (walking, driving or biking) or undergo centrifugation (Woellner and Graybiel, 1959; Miller and Graybiel, 1971; MacDougall et al., 1999). The OCR tends to orient the eyes towards the GIA. The ability to complete the orientation is thought to be crucial for our postural stability during movements (Imai et al., 2001).

**Spaceflight.** The importance of the vestibular system, as well as the importance of gravity, for our ability to maintain balance becomes particularly clear when studied in relation to spaceflight. When orbiting around Earth, the space crew inside the International Space Station (ISS) is in a so-called “free fall”, meaning that instead of the 1g-gravity environment humans experience on Earth, the gravity is reduced to $10^{-6}$ g, i.e. microgravity. The vestibular receptors (the utricle and saccule) are the primary gravity sensors of the body and their gravity dependence makes them especially vulnerable in a microgravity environment. In the absence of gravitational inputs, the otoliths will be forced to adapt to the new condition to be able to orient in space (Clarke et al., 2000). During the adaptation process, a deconditioning (decrease in gain of otolith-mediated reflex) of the otolith system is thought to take place, which is hypothesized to be the cause of several of the symptoms reported in returning astronauts, such as balance problems and dizziness. (Homick and Reschke, 1977; Young et al., 1984; Anderson et al., 1986; Reschke et al., 1986; Paloski et al., 1992; Dai et al., 1994; Clement and Reschke, 1996) When the astronauts re-enter the gravitational environment on Earth, a majority of them experience, among others,
orthostatic intolerance (OI) and spatial disorientation as well as gaze control problems (Buckey et al., 1996; Fritsch-Yelle et al., 1996). Several studies have shown an activation of sympathetic outflow in response to postural changes and therefore, the otolith system is also hypothesized to be important in the prevention of OI (Yates et al., 2014). A recent study has added evidence to the link between the vestibular and the autonomic system (Hallgren et al., 2015).

What has been done until now. Since OCR is an accepted way to evaluate the condition of the otolith system (Clement and Reschke, 1996), a number of studies have used the OCR as a measurement of the effect of microgravity on the vestibular system (Yakovleva IY, Kornilova LN, Serix GD, Tarasov IK, 1982; Arrott and Young, 1986; Vogel and Kass, 1986; Hofstetter-Degen et al., 1993; Diamond and Markham, 1998; Young and Sinha, 1998). However, there are contradicting results from studies showing an increase, a decrease or no change in OCR on return compared to before flight. Clément and colleagues wrote a review covering all OCR data induced by static whole body tilt after (short-term) shuttle missions in 2007. The 18 astronauts showed no significant change in OCR postflight compared to preflight (Clément et al., 2007). An important limitation of the studies evaluating centrifuge-induced OCR so far is the fact that all researchers investigated a small sample size, mostly due to the overall difficulty and restrictions to astronaut access. In addition, the abovementioned results mostly come from short-term spaceflight, which makes it difficult to generalize around the effect of long-term exposure to microgravity. More recently, a couple of studies focusing on OCR induced by head tilt, the so-called static torsional otolith-cervical-ocular reflex (OCOR), have been performed by Kornilova and colleagues. They concluded that the otolith function was suppressed early after
spaceflight, and that it recovered within 8-9 days (Kornilova et al., 2007, 2011, 2012).

**Aim of the study.** The aim of the current study was to investigate if long-term exposure to microgravity results in changes in the otolith-mediated response OCR, in returning astronauts. As hypothesized, a possible otolith de-conditioning could be responsible for a number of negative effects seen in returning astronauts (see the paragraph *Spaceflight* above). We aimed to collect sufficient data to make more convincing conclusions concerning the effect of spaceflight on the OCR response. With a bigger sample size, we were also able to look into to the more subtle physiological effects. That could be learning effects due to space flight experience and adaptation, as well as possible differences in OCR response between the two directions of rotations during centrifugation.

**Methods**

We measured the otolith mediated OCR response induced by centrifugation in a space crew before and after spaceflight to evaluate the otolith mediated vestibular reflex. We conducted our experiments in the Gagarin Cosmonaut Training Centre (Star City) near Moscow, Russia. A group of 25 (24 male and 1 female) cosmonauts (average age of 46, SD ± 6 years) from the Russian Space Agency (Roscosmos) and one from European Space Agency (ESA) (all denoted as astronauts) took part in the study. The astronauts were tested before and after a 6-month stay in the International Space Station (ISS). The average number of days spent in space was 164 (SD ± 22). The first astronaut participating in the study was tested in 2007 (ISS expedition 16) and
the last one in 2015 (expedition 43). The preflight data was based on two baseline experiments (baseline data collections; BDCs) that were conducted on average 55 (SD ± 29) days before launch. The astronauts were tested again two to three times postflight. The first postflight experiment took place 2-3 days after return (R+2/3), the second one 4-5 days (R+4/5) and the last one 9-10 days after return (R+9/10). Due to medical and organizational issues, we were not able to test all the astronauts on the exact same day after return. On average, the first measurement took place 3.6 days (SD ± 1.2 days) after return back to Earth.

All participants provided written informed consent prior to their participation. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of European Space Agency (ESA), the Antwerp University Hospital and Roscosmos.

**VVIS – evaluation of the otolith system.** For the experiment, the subject was seated in the Visual and Vestibular Investigation System (VVIS), a small centrifuge (rotation chair, see figure 1) built for the Neurolab shuttle mission. The astronaut was securely fixed in the chair and head movements were restricted. The entire room was darkened to avoid visual motion feedback during rotation. The centrifuge allowed earth vertical rotation on a fixed distance of 0.5m from the axis of rotation. In front of the astronaut, a screen was placed on which visual targets were present during parts of the experiments. After calibration of the video-goggles and a baseline recording, the astronaut was subjected to 1g for 5 minutes in a counter clockwise (CCW) and 5 minutes in clockwise (CW) direction subsequently. The rotation was always performed first in CCW and then CW direction with a short pause in between (when
the chair was turned around). The subject was facing the direction of motion for both CCW and CW rotation. Right-ear out (REO) during CCW rotation and left-ear out (LEO) during CW. The maximum velocity of 254°/s was chosen to obtain a centripetal acceleration of 1g outwards. Combined with gravity, such a shear force constitutes a virtual sideways tilt of 45 degrees (θ=45° in figure 1), inducing an OCR of typically 5 to 7 degrees, given a OCR gain of approximately 15% in normal conditions (Collewijn et al., 1985).

Measurements of the OCR were taken before and during rotation according to a fixed protocol. The first measurement was taken during stand-still, which meant no centripetal force acting on the body and an expected OCR of 0°. The second measurement was taken 40 seconds after the stable phase of rotation was reached. The 40 seconds of delay was implemented to allow the cupula of the horizontal semicircular canal to return to its original position, to make sure the measured OCR was based on contribution of the otolith system only. During the 20 seconds period the OCR was measured, the subject observed a fixation dot that was visible on the screen in front of the subject. The dot was implemented to suppress other eye movements, such as saccades, during centrifugation. The OCR value was calculated as the average eye torsion over the 20 second long recording (see example of raw OCR data in figure 2). The recording consisted of between approximately 600-1000 frames representing a data point each. In addition, the standard deviation and the standard error of the OCR response was calculated for all the frames for every experiment. The difference in OCR between standstill and rotation was defined as the OCR outcome value, the "ΔOCR". The preflight data, ΔOCR_{preflight}, was compared with the ΔOCR’s recorded on return, the ΔOCR_{postflight}. The difference in ΔOCR
Preflight versus postflight gave us an indication of the influence of microgravity on the otolith-mediated vestibular response. (We will use the notation OCR during the rest of the article, always referring to the difference between standstill and rotation).

We recorded the induced OCR during the experiment using three-dimensional infrared video-oculography (Moore et al., 1996).

**Statistics.** The video files containing recordings of the eye movements were analyzed to calculate the torsion of the eyes, i.e. the OCR. To do this, we ran the files in a visual programming language. The program we used was custom made in National Instruments LabVIEW by one of the co-authors. Example of raw OCR data for one subject (left eye, CCW rotation) can be found in figure 2. Figure 2a shows a preflight measurement and 2b a corresponding plot with postflight data. Further statistical analyses were made in R (version 3.1.2) and Excel. To model the change in OCR between the preflight and the postflight measurements, a linear mixed model was fitted with the OCR as dependent variable. Time (BDC, R+2/3, R+4/5 and R+9/10), direction of rotation (CCW and CW) and eye (left and right) were chosen as fixed factors, and in addition a random intercept for individuals was introduced, to account for the dependence between observations within the same individual. Each OCR observation represents the average of a recording lasting up to 20 seconds. The 20 seconds consist of approximately 1000 frames, each frame representing one OCR value. We calculated an average and standard deviation of OCR over all those frames. Due to blinking and closed eyes not all the frames could be used for all subjects. The median number of frames that could be used for calculation of the average OCR was 815 frames, with median absolute deviation of 185. To take the individual variance
into account we weighted each OCR observation by the inverse of its variance. Time was entered as a categorical variable with 4 levels: BDC, R+2/3, R+4/5 and R+9/10. The two other independent variables (eye and rotation) were also categorical. Significance of the fixed effects was tested using an F-test with Kenward-Roger correction for the number of degrees of freedom. An F-test is superior to an asymptotic chi-square test for investigating the significance of the fixed effects in a linear mixed model, but this needs a balanced study design (i.e. the same number of observations within each group and at each time point). When this balance requirement cannot be met in practice, the Kenward-Roger correction on the number of degrees of freedom is recommended to obtain valid inferences based upon the F statistic (Halekoh and Højsgaard, 2014). A post-hoc analysis, to test if pairwise differences in OCR between preflight and postflight time points were significant, was carried out using a Dunnett correction for multiple comparisons with the preflight time point as reference level.

Results

Differences in OCR at the different time points. To model the change in OCR following a space flight, a linear mixed model of OCR versus time was fitted, as described in the methods section, with time including all 4 time points (1= (BDC), 2=(R+2/3), 3=(R+4/5), 4=last experiment postflight (R+9/10)). Not all astronauts were available for testing three times postflight, due to the evident restrictions in astronaut schedule and access. Therefore, the first postflight measurement was either 2-3 days (one astronaut was tested on R+1) or 4-5 days after re-entry. The linear mixed model showed a highly significant effect of time on the OCR (p<0.001).
post-hoc analysis, comparing OCR preflight with OCR at the 3 postflight time points, showed a statistically significant decrease in OCR at R+2/3 and at R+4/5. At R+9/10, there was no longer a difference in OCR compared to preflight OCR values. In table 1, the OCR values, including standard deviation and standard error, can be found.

Out of the 25 subjects, 19 had a decreased OCR postflight, 3 had no or a very small change and one of them had an increase in OCR after spaceflight. Two out of the 25 subjects were not available for testing R+2/3 or at R+4/5, due to complications. For those two, we only have preflight data and OCR data from R+9/10. For comparison purpose, we also report the gain (see table 1). This was computed by dividing all OCR values by 45 degrees, being the tilt of the GIA.

Figure 3 shows the mean values of OCR (including standard error) for the 4 time points, averaged over directions and eyes. The figure displays the OCR for the preflight experiment (6.99°± 0.66°), as well as for the three postflight experiments. Figure 4a and 4b show the average raw OCR data response grouped according to the direction of rotation. In each diagram, i.e. for each rotation, the recorded OCR of the two eyes is also individually presented.

Table 1 about here

Figure 4a and 4b about here
Differences in OCR between the two directions of rotations. During the centrifugation, the subject was always rotated first CCW and then in CW direction, with a short pause in between. When comparing the OCR data from the two directions of rotations for the preflight experiment, using the linear mixed model, we observed a significantly higher OCR for the CCW (first direction of) rotation. The recorded OCR value was 0.57° (SE = 0.22°, p=0.008) lower during CW rotation compared with the one recorded during CCW rotation. For the postflight experiments, no significant difference between the rotation directions was found.

First-time flyers versus experienced flyers. Out of the 25 astronauts, 13 were first-time flyers and 12 had been flying at least once prior to our study, with 2 of them already flying 4 times before participating in our experiment. We compared OCR versus the flight experience for the two groups using the linear mixed model. We saw a trend in the difference in OCR between the two groups. The OCR was consistently lower, across all time points, for the group of experienced flyers compared to the first time flyers, but at none of the time points this difference was significant. A model across all time points gave an OCR that was on average 0.99° lower (SE ± 0.68°) for the experienced fliers (p>0.05).

Discussions

The effect of microgravity on the OCR reflex. The aim of this study was to investigate the effect of long-term exposure to microgravity on the otolith-mediated vestibular response in a considerably large group of 25 astronauts returning from the ISS after 6 month missions. Our main finding was that the OCR response was
significantly decreased early after spaceflight (at R+2/3 and R+4/5). This indicates that the otolith-mediated vestibular response among the astronauts was affected during the first days after return, likely due to the absence of gravitational input during the preceding 6 months. A recording of a lower OCR after spaceflight agrees with a number of studies performed in the last decades (Dai et al., 1994; Diamond and Markham, 1998; Young and Sinha, 1998; Moore et al., 2005; Kornilova et al., 2012). Clément and colleagues found no significant change in OCR postflight compared to preflight in 18 astronauts tested after (short-term) shuttle missions (Clément et al., 2007). A possible reason for this could be the duration of the shuttle missions lasting less than two weeks, while the data collected in the current study covers astronauts who spend 6 months in space. Another difference, however, may be due to the difference in vestibular stimulation between static tilt (which elicits response from the vertical semi-circular canals) and centrifugation (which does not). An important limitation of the studies evaluating centrifuge-induced OCR so far is the fact that all investigated a small sample size, which has made generalization difficult. Kornilova and colleagues (Kornilova et al., 2012), measured static torsional otolith-cervical-ocular reflex (OCOR) in 17 cosmonauts before and after spaceflight. From the 17 subjects; 7 of the subjects had a 50% decrease of OCOR at the first day after return (R+1 or R+2), in 3 of them a reversed OCOR was measured, in 4 of them no OCOR was registered and 3 subjects showed no difference between the pre- and postflight OCOR. The results for OCOR presented by Kornilova and colleagues showed a gain of 0.21 preflight and 0.11, 0.15 and 0.22 for the three postflight time points respectively (with the absolute values: 6.59°, 2.94°, 4.25° and 6.81°). Our results, reported in table 1, show a preflight gain of 0.15, and postflight OCR gains of 0.12, 0.13 and 0.16. This suggests that when proprioceptive input from the neck
afferents is available, the response to tilt seems enhanced, at least during the period when microgravity effects are not dominant. The current experiment differs from previous experiments by Kornilova in the fact that no neck influence is present in the centrifugation paradigm, where all subjects are seated upright with head fixed in the vertical position. Consequently, no proprioceptive afferent input is given to the vestibular system. In order to solely study the otolith mediated response and the effect of microgravity, centrifugation appears to be a more pure stimulus.

Moreover, no previous study covered as many as 25 astronauts returning from a 6-month stay in space. The strong significance of the decreased OCR adds to the evidence that microgravity causes adaptive changes in the otolith-mediated vestibular response. At the last postflight experiment, 9 days after return, there was no longer a significant difference of the measured OCR response compared to the preflight values. This suggests that the OCR reflex was back at baseline level and that the otolith mediated system was fully recovered, which agrees with the results of Kornilova (Kornilova et al., 2012). This delay in adaptation of the otolith mediated vestibular response can have negative consequences for the astronauts when re-entering gravity. In our study, we were not able to correlate the change in OCR with any of those parameters associated with disequilibrium. Entering another gravitational environment than the one here on Earth, such as for example Martian gravity, while not being able to fully function during the first days after landing may have severe consequences for the crew. There will be no room for mistakes during a recovery period. Preferably, it would not be necessary to recover, if the cause (lack of gravity) could be removed in the first place. The current data suggest a recovery rate of a little over one week, but this reflects the vestibular response. A recent single case study
however has shown that even 9 days after return, an astronaut still showed alterations in the cortical vestibular network, as measured by means of functional MRI (Demertzi et al., 2015). This suggests that the underlying neural adaptation takes longer than is seen in the vestibular reflex based on peripheral end organs, e.g. the otoliths. Evidently, this has to be further investigated in a larger sample size, but the question arises where the impact of microgravity takes place, i.e. on the peripheral end organ at the level of the otoliths or more centrally?

**Differences in OCR between the two directions of rotations.** The OCR response was found to be higher during the CCW (first rotation), than for the recording during the CW rotation, which could be a consequence of habituation. During postflight experiments, the difference was no longer significant between the two tests (CCW and CW). It could be speculated that a difference in OCR between the two rotations was still present, but due to the lower postflight OCR values the difference was too small to detect. Up front, we didn’t expect to find a difference in OCR between the two directions. To our knowledge, this has not been seen in previous studies. To make any conclusion concerning a learning effect, further testing would be necessary, preferably with a counterbalanced order of the two directions of rotation.

**Experienced flyers.** Even though the mean OCR was consistently lower across all time points for the group of experienced flyers, for none of the time points this difference was significant. Within both groups, the variance in OCR was large, so even if a lower OCR was observed, the p-value was not significant. Moreover, the large variance is likely due to the fact that the experienced flyers’ group was a heterogeneous mixture of second, third and fourth time flyers. Preferably, the same
subject should be measured at least twice, first as a first time flyer and then again as
an experienced flyer. From a study design point of view, the pairwise tests within
subjects are a much stronger and more powerful analysis as each subject acts as its
own control. Therefore, we can’t exclude that flight experience can have a significant
influence on the OCR response. A test re-test study, with the same subject is currently
ongoing to further investigate this phenomenon.

Countermeasures. One suggested way to counteract negative effects related to
spaceflight is to create artificial gravity in space (Moore et al., 2001; Clément et al.,
2015). This could also be an efficient solution when it comes to the otolith-based
problems. If stimulating the otolith system with artificial gravity during spaceflight
could prevent adaptation, we might not see those problems upon return. After the 16-
day long NASA-led Neurolab mission in 1998, the artificial gravity hypothesis was
presented. Four crewmembers were exposed to artificial gravity by means of
centrifugation during spaceflight. It turned out that the magnitude of the OCR reflex
was maintained throughout the flight as well as on return. (Moore et al., 2005).

However in 2007, Clément and colleagues reviewed the OCR response in 18
astronauts retuning from 6 different short-term shuttle missions (Clément et al., 2007).
They didn’t find any change in OCR response even without in-flight centrifugation. It
is important though to keep in mind that the shuttle missions are short-term flights, in
comparison with the 165 days our subjects on average spent in space. The number of
subjects was also much smaller than used in our study. To make further
recommendations concerning artificial gravity as a countermeasure against a
decreased otolith function, further testing needs to be done, preferably evaluating
artificial gravity during long-term spaceflights.
Conclusion. After a long-term exposure to microgravity, the otolith-mediated vestibular response among returning astronauts was highly affected. The OCR reflex was significantly decreased in the 25 astronauts taking part in the study. Nine days after return, the OCR was back at preflight values, indicating a full recovery of the peripheral otolith system. During this study, sufficient data has been collected to make general physiological conclusions about the effect of microgravity on the otolith system.

Acknowledgement

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References


Clément G, Denise P, Reschke MF, Wood SJ. Human ocular counter-rolling and


Kornilova L.N., Temnikova V.V. SSV et al. Effect of otoliths upon function of the semicircular canals after long-term stay under conditions of microgravitation. *Russ


Young LR, Sinha P. Spaceflight influences on ocular counterrolling and other

Captions:

**Figure 1:** The Visual and Vestibular Investigation System (VVIS) chair

During off-axis centrifugation, the net linear acceleration stimulating the otoliths is the vector sum of the centripetal force and gravity, i.e. the GIA. The vector sum can be found in the figure. The gravity vector is pictured pointing upwards (as a balancing force) to visualize the tilt illusion sensed during centrifugation. When the GIA is interpreted as the spatial vertical, the subject experiences a sensation of tilt. In this case, the constant force of gravity together with centripetal force, each of them 1g, gives a perceived tilt of 45°. "Reprinted by permission from Macmillan Publishers Ltd: SCIENTIFIC REPORTS (Hallgren et al., 2015), copyright (2015)"

**Figure 2:** Example of raw OCR data for one subject, preflight and early postflight

Figure 2a shows an example of OCR raw data for one of the subjects, recorded preflight, left eye CCW rotation. 2b shows OCR raw data for the same subject early postflight. This is how the data looks like when extracted from the video files in Labview. The x-axis shows the time in seconds.

**Figure 3:** Change in OCR response, preflight compared to postflight

The figure shows, the weighted OCR data, averaged over eyes and rotation. The OCR response is expressed in degrees and presented with the weighted standard error. The first measurement was performed prior to spaceflight and the last three experiments were performed postflight. The first postflight experiment took place 2-3 days after return, the second one 4-5 days after and the late postflight 9-10 days after return from a 6-month stay in the ISS. The day on which the experiment took place is presented on the x-axes. At the preflight experiment, the BDC, all the 25 subjects were available for testing. 12 of the subjects were tested at R+2/3, 21 of them at R+4/5 and 22 at R+9/10. At the R+2/3 the OCR was 2.21° (SE=0.20°) degrees lower compared to the preflight OCR, a significant decrease in OCR response (p<0.001). 9 days after return, during the late postflight experiment, the OCR returned back to preflight values.

**Figure 4:** Alteration of OCR for the two directions of rotation and the two eyes separately

Figure 4 shows the mean raw OCR values for the two directions of rotation divided into two graphs. Each of the graphs represents the OCR for the two eyes separately. The mean raw OCR data is plotted together with the standard error. 4a shows the average OCR for the first direction of rotation, the CCW rotation, for the 25 astronauts. 4b shows the average OCR for the second direction of rotation, the CW rotation, for the 25 astronauts. The pure raw data (and not the mean OCR) has been analyzed using a linear mixed model to investigate if there were any differences in OCR between the two direction of rotation and between the two eyes.

**Table 1:** The weighted OCR data, pre- and post-flight

<table>
<thead>
<tr>
<th>Day of Return</th>
<th>OCR (°)</th>
<th>SE (°)</th>
<th>SD (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-flight</td>
<td>6.99</td>
<td>0.66</td>
<td>0.54</td>
</tr>
<tr>
<td>R+2/3</td>
<td>5.99</td>
<td>0.57</td>
<td>0.47</td>
</tr>
<tr>
<td>R+4/5</td>
<td>5.99</td>
<td>0.57</td>
<td>0.47</td>
</tr>
</tbody>
</table>

The OCR was significantly lower compared to preflight measurements. At the R+4/5 experiments, if available, the OCR was 5.99° (SE=0.57°). 9 days after return, on the day of the late postflight experiment, the difference with the preflight value was no longer significant, indicating a recovery of the otolith system.
Experiment day

OCR (degrees)
<table>
<thead>
<tr>
<th></th>
<th>OCR</th>
<th>SD</th>
<th>SE</th>
<th>Gain</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDC</td>
<td>6.99°</td>
<td>1.99</td>
<td>0.66</td>
<td>0.15 ±0.06</td>
<td>25</td>
</tr>
<tr>
<td>R+2/3</td>
<td>5.33°</td>
<td>2.34</td>
<td>0.78</td>
<td>0.12 ±0.06</td>
<td>12</td>
</tr>
<tr>
<td>R+4/5</td>
<td>5.99°</td>
<td>1.71</td>
<td>0.57</td>
<td>0.13 ±0.05</td>
<td>21</td>
</tr>
<tr>
<td>R+9/10</td>
<td>7.17°</td>
<td>2.19</td>
<td>0.73</td>
<td>0.16 ±0.05</td>
<td>22</td>
</tr>
</tbody>
</table>
Experiment day

OCR (degrees)

CCW rotation

Left eye

Right eye

BDC

R+2/3

R+4/5

R+9/10