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Vestibular Function and Space Motion Sickness

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Abstract—The vestibular system plays an important role in intersensory interactions and gravitation is a natural stimulus for its receptors. Weightlessness alters the input signals of the otoliths and their effect on the pattern and dynamics of changes in the vestibular function (VF), which is accompanied by development of space adaptation syndrome (SAS) and space motion sickness (SMS). These changes occur both during the spaceflight (SF) and after returning to Earth, but the mechanisms of their development are still poorly understood and require special studies. In total, 47 Russian cosmonauts (crewmembers of long-term International Space Station (ISS) missions) have participated in the studies into VF before and after SF and nine of them, in onboard studies during SF (129–215 days) as a part of the Virtual space experiment (stage 1). Electro- and video-oculography are used to record spontaneous eye movements (SpEM), static vestibular–ocular responses during head tilts to the right or left shoulder (static otolith–cervical–ocular reflex, OCOR), and dynamic vestibular-ocular response during the head rotation around the longitudinal axis of the body. The examination is accompanied by personal and questionnaire survey on subjective responses and complaints of cosmonauts about SAS and SMS. Significant changes in SpEM (drifts of eyes, spontaneous and gaze-evoked nystagmus, and arbitrary saccades) and a decrease in OCOR (statistically significant decrease in the amplitude of ocular counter-rolling in response to head tilts up to its absence or inversion, an atypical OCOR) are observed during SF. An atypical OCOR is observed at the beginning of adaptation to weightlessness in seven of the nine cosmonauts (the first one to two weeks of SF) and repeatedly throughout the flight in all cosmonauts regardless of whether it is their first flight or not. Atypical vestibular responses after SF, similar to the responses during SF, are observed in several cosmonauts by day 9 after flight. It has been shown that atypical OCOR variants are more frequently observed in the subjects lacking any previous space experience, as well as a more pronounced decrease in this response with a concurrent increase in the response of the semicircular canals. It is also demonstrated that repeated SFs lead to a considerable shortening in the after-flight readaptation to terrestrial conditions and a considerable decrease in the degree of vestibular disorders. In the initial period of SF, the changes in VF are correlated with the complaints and manifestations of SAS and SMS; however, the complaints and the corresponding symptoms are unobservable during the further flight despite significant changes in the VF state. The patterns of the VF disorders associated with the impact of weightlessness and observed during and after SF are very similar, allowing these disorders to be regarded as SAS and SMS of different severities (intensities).

Keywords: static torsion otolith–cervical–ocular reflex, dynamic vestibular-ocular responses, spontaneous eye movements, space adaptation syndrome, space motion sickness, weightlessness, repeated spaceflight

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A retrospective analysis of the results of spontaneous oculomotor and illusory responses and the responses induced by their optokinetic and vestibular stimulation in weightlessness in the Mir and Salyut space stations and after space flights (SFs) performed under the programs of Russian experiments (ANKETA, OPTOKINEZ, and OKULOSTIM), Bulgarian–Russian (LABIRINT and LABIRINT-2), Austrian–Russian (OPTOVERT and OPTOVERT-2), and German–Russian (VOG) [1–3] experiments has made it possible to systematize for the first time the phenomenology of the symptoms of atypical sensomotoric responses of the body to new environment and ascribe them to a specific “space” adaptation syndrome (SAS) or to space motion sickness (SMS).

The very first studies of the effect of weightlessness on the human vestibular function (VF) were performed by Young et al. [4], von Baumgarten et al. [5], Watt et al. [6], Clement et al. [7], Thornton et al. [8], Kornilova et al. [1, 2, 9], Moore et al. [10], Reschke et al. [11], and Clarke et al. [12]. However, the results were obtained for the groups not exceeding four astronauts as well as were rather contradictory and allowed neither assessment of statistical significance of the observed changes nor any concept of the effect of long-term weightlessness on VF; in addition, the effect of repeated SFs was not considered and the patterns and dynamics of VF function during weightlessness and after SF during readaptation were not compared, in particular, the changes in otolith-ocular and canal-ocular reflexes as well as their association with SAS and SMS.

All these facts determine an undiminished interest of researchers to this area and the need in conducting the first stage of space experiment named Virtual in the Russian segment of the International Space Station (ISS).

The goals of the first stage of the experiment were

—to study the effect of long-term weightlessness on the state of VF during SF and readaptation to terrestrial conditions;

—to assess the effect of repeated SFs on the VF characteristics during the flight and postflight readaptation;

—to analyze and compare the dynamics of the changes in VF in weightlessness and post-SF readaptation to terrestrial conditions;

—to analyze and compare the static otolith–ocular and dynamic canal–ocular reflexes after long-term SFs; and

—to analyze and compare the changes in VF and subjective complaints about SMS during adaptation to weightlessness, SFs, and readaptation to terrestrial conditions.

METHODS

According to the program of the Virtual space experiment (stage 1), 47 Russian cosmonauts, crewmembers of long-term ISS missions (SFs of 129 to 215 days), were examined. Nine of the 47 cosmonauts were examined onboard during SF along with the pre- and post-SF examinations (age of the subjects from 35 to 50 years old; average age, ~44 years).

The examined subjects were divided into two groups: group I comprised 26 subjects experiencing weightlessness for the first time (four of them participated in the onboard examination) and group II comprised 21 subjects with the previous SF experience (five of them participated in the onboard examination).

All subjects were examined two times before SF (background); nine of them, during SF on days 2, 5, 15, and 30 and then on a monthly basis (each subject was examined eight to nine times during SF); and all of them were examined on days 1–2, 4–5, and 8–9 after landing (in some cases, also on days 13–19).

The VF state was assessed according to vestibular-ocular reflexes using video-oculography (VOG). In some cases, electro-oculography (EOG) was additionally used during pre- and post-SF examinations.

VOG was used to examine spontaneous eye movements (SpEM), static torsion otolith-cervical-ocular reflex (OCOR), dynamic vestibular–cervical–ocular reflex (VCOR), and vestibular reactivity (VR).

SpEM were recorded when the head was in an upright vertical position fixed using a cervical collar. Drift and saccadic eye movements were recorded, as well as spontaneous nystagmus with the central position of the eyeballs and their rightward–leftward and upward–downward shifts after an audio signal. The eyes were kept at each position for 7 s.

OCOR was assessed according to the amplitude of the compensatory torsional ocular counter-rolling in response to head tilt after the audio signal alternatively to the right and left shoulders to an angle of 30°. In order to exclude any dynamic effects on the static reflex, the tilt position of the head was retained for 16 s. The tilt angle was controlled with specialized angle meter and recorded with helmet detectors of the VOG complex.

VCOR was assessed according to the gain as the ratio of the velocity of compensatory horizontal ocular counter-rolling to the velocity of the head rotation along the body longitudinal axis at a frequency of 0.125 Hz with the eyes open and closed. The examined subject initially held the head maximally turned to the right shoulder. After the audio signal, the subject slowly (during the entire signal, 4 s) moved the head to the left shoulder to the leftmost position. When the signal tone changed, the subject turned the head to the right shoulder during the entire signal (4 s) to reach the initial position. The number of the head movements was six to nine depending on the subject's well-being.

VR was estimated according to the duration and intensity of vestibular-induced nystagmus on the background of the response of horizontal compensatory ocular counter-rolling during the head rotation around the longitudinal body axis with a frequency of 0.125 Hz. The presence of solitary nystagmic beats during the test taking up to 15% of its duration indicated a normal VR, while an increase or absence of nystagmus suggested an increase or a decrease in VR.

The questionnaire (ANKETA) was used when examining the cosmonauts to assess their subjective state relative to the set of SMS symptoms. The SMS symptoms comprised the complaints about orientation illusions, dizziness, discoordination, and difficulties in fixation and tracing visual objects, nausea, and vomiting. The set, intensity, and duration of these responses were assessed using the classification accepted in Russia [2, 3]: 0, no complaints of SMS symptoms; 1, complaints of moderately pronounced and rather short SMS syndrome; and 2, complaints of pronounced and long SMS syndrome with strong dizziness, vomiting, and discoordination.

A VOG complex (Chronos Vision ETD, Berlin, Germany) [9, 12], was used to record the horizontal, vertical, and torsional eye movements. A helmet equipped with high-frequency infrared video cameras (for recording eye movements) and angular velocity sensors and accelerometers (for recording head movements) was put on the subject's head. The eye movements were recorded in the range of up to 55° horizontally and to 35° vertically. The video-oculography recording rate was 200 fps. The VOG records were processed with the help of the ETD IrisTracker software with a recognition accuracy of $<0.05°$.

The following characteristics were evaluated when processing the VOG recordings: the amplitude of compensatory torsional ocular counter-rolling at a static head position after a tilt to the shoulder (the amplitude was estimated at 14–16 s after the tilt); gain of OCOR (ratio of the amplitudes of the torsional ocular counter-rolling and head tilt, gOCOR); nystagmic response of spontaneous eye movements during the head rotation long the longitudinal body axis (time, amplitude, velocity, and frequency characteristics of nystagmus, including the amplitude of nystagmus rapid phase, A_{Ny} (angular degrees); velocity of nystagmus slow phase; V_{Ny} (degrees per second); nystagmus frequency, F_{Ny} (hertz); and nystagmus relative duration T_{Ny} (percent); i.e., the ratio of total duration of nystagmic cycles to total test duration).

The quantitative estimate and comparative analysis of VF characteristics were performed by parametric and nonparametric ANOVA and correlation analysis. Mathematical expectation, variance, variation range, and variation coefficient were assessed for each characteristic. The critical level of significance α was 0.05 for all cases of statistical hypothesis testing (normality of distribution, homogeneity of variance, statistical significance of differences, etc.). The following methods were used to test the hypotheses on the presence of statistically significant differences in the characteristics before, during, and after SF: the F test (ANOVA) with Tukey's multiple (pairwise) comparisons; Friedman test (ANOVA) with pairwise comparisons by Wilcoxon's test with Bonferroni's adjustment; and U test (Mann–Whitney test) for between-group comparison.

Normality of distributions was verified by Kolmogorov–Smirnov Lilliefors test and homogeneity of variances, by Levene's test.

RESULTS

Spontaneous eye movements (SpEM). Before SF, gaze-evoked nystagmus was recorded only in one cosmonaut of group I (first SF) ($A_{Ny} = 2.5 \pm 0.3°$; $V_{Ny} = 4.3 \pm 0.8°/s$; $F_{Ny} = 0.5 \pm 0.04$ Hz).

The dynamics of SpEM and SMS are shown in Table 1. As is evident from Table 1, all subjects displayed SpEM disturbances during the initial period of adaptation to weightlessness (days 2–15 of SF), which appeared either as spontaneous nystagmus in the case of the central gaze and gaze-evoked nystagmus when looking aside or as an increase in saccadic activity, prevalently of a quadrangular shape, the so-called square-wave jerks. On days 2–5 of adaptation to weightlessness, cosmonauts reported development of SMS symptoms of different degrees, (1) or (2).

No differences were observed in the SpEM patterns in the subjects without and with previous SF experience. The SpEM of only six of the nine examined cosmonauts on day 30 of SF were the same as before the flight (background). In the subsequent SF period, either an increase in SpEM or typical and atypical nystagmus was observed in the subjects that displayed normalization, i.e., adaptation was replaced by a period of disadaptation. However, any SMS symptoms were unobservable during disadaptation periods. No dependence of SpEM on the previous SF experience was detected. Cyclic patterns of adaptation/disadaptation periods in the subjects were individual and independent on whether the flight was the first or not.

Figure 1 shows the native curves illustrating SpEM before and after SF.

The native curves in Fig. 1 show a drastic increase in SpEM during SF to appearance of the cycles of spontaneous nystagmic eye movements.

Analysis of SpEM after SF demonstrated statistically significant differences between the groups of cosmonauts without and with previous SF experience.

The evaluation of SpEM and SMS symptoms before and after SF in groups I and II is detailed in Table 2.

As is evident from Table 2, 22% of the subjects of group I (first SF) on days 1–2 after SF displayed normal SpEM; 33%, an increase in SpEM as slow wave drifts or saccadic eye movements (square wave jerks); and the remaining 45%, spontaneous nystagmus ($A_{Ny} = 3.8 \pm 0.6°$; $V_{Ny} = 6.5 \pm 0.8°/s$; $F_{Ny} = 1.5 \pm 0.1$ Hz; $T_{Ny} = 18.6 \pm 7.1\%$) and gaze-evoked nystagmus ($A_{Ny} = 3.1 \pm 0.7°$; $V_{Ny} = 3.7 \pm 0.8°/s$; $F_{Ny} = 0.6 \pm 0.1$ Hz; $T_{Ny} = 34.9 \pm 12.5\%$). On days 1–2 of readaptation period, 69% of the subjects in this group complained of SMS symptoms, moderate or pronounced.

As for group II (subjects that repeatedly experienced long-term SF), 58% displayed normal SpEM on days 1–2 after flight; 21%, increase in SpEM; and remaining 21%, spontaneous nystagmus ($A_{Ny} = 4.1 \pm 0.9°$; $V_{Ny} = 6.2 \pm 1.0°/s$; $F_{Ny} = 1.3 \pm 0.1$ Hz; $T_{Ny} = 12.3 \pm 8.6\%$) and gaze-evoked nystagmus ($A_{Ny} = 3.3 \pm 0.8°$; $V_{Ny} = 3.8 \pm 0.9°/s$; $F_{Ny} = 0.7 \pm 0.1$ Hz; $T_{Ny} = 22.4 \pm 9.0\%$). Moderate SMS symptoms were observed on days 1–2 of readaptation in 33% of group II subjects.

It is evident from Table 2 that the most pronounced and longest retained SpEM changes were observed in the group of cosmonauts after their first SF versus the group II of the subjects previously experienced SF (79% displayed SpEM restoration as early as day 4 after SF).

Table 1. Dynamics of SpEM and SMS disorders in space flight

Cosmonaut	Days of testing (*L,* baseline and *F,* days of flight)								
	L-60–30	*F*-2	*F*-5	*F*-15	*F*-30	*F*-60	*F*-90	*F*-120	*F*-150
First SF (*n* = 4)									
C1	–	Sp Ny (2)	Sp Ny (1)	+ (0)	– (0)	Sp Ny (0)	Sp Ny (0)	– (0)	+ (0)
C2		+ (1)	Sp Ny (1)	Sp Ny (0)	+ (0)	Sp Ny (0)	– (0)	+ (0)	– (0)
C3		Sp Ny (2)	Sp Ny (1)	Sp Ny (0)	– (0)	– (0)	– (0)	Sp Ny (0)	– (0)
C4		Sp Ny (1)	+ (1)	– (0)	– (0)	+ (0)	+ (0)	– (0)	– (0)
Repeated SF (*n* = 5)									
C5	–	Sp Ny (1)	Sp Ny (1)	– (0)	+ (0)	– (0)	– (0)	– (0)	– (0)
C6		+ (1)	Sp Ny (1)	Sp Ny (0)	– (0)	– (0)	Sp Ny (0)	– (0)	+ (0)
C7		Sp Ny (1)	Sp Ny (1)	+ (0)	– (0)	+ (0)	+ (0)	– (0)	– (0)
C8		+ (1)	Sp Ny (1)	– (0)	+ (0)	Sp Ny (0)	– (0)	– (0)	– (0)
C9		+ (1)	+ (1)	+ (0)	– (0)	– (0)	+ (0)	– (0)	– (0)

(–) Norm, no abnormalities; (+) increase in saccadic activity, mainly, eye square-wave jerks, drifts, and “gliding” gaze; Sp Ny, spontaneous nystagmus; and (0)–(2) scores of complaints about SMS (for classification, see Methods).

Table 2. Assessment of SpEM and SMS symptoms before and after space flights

Group of cosmonauts	Days of testing (*L,* baseline and *R,* days after flight)			
	L – 60–30	*R* + 1–2	*R* + 4–5	*R* + 8–9
Group I (*n* = 26)	Normal, 96% Increased SpEM, 4%	Normal, 22% Increased SpEM, 33% Spontaneous Ny, 45% SMS symptoms, 69%	Normal, 50% Increased SpEM, 28% Spontaneous Ny, 22% SMS symptoms, 22%	Normal, 67% Increased SpEM, 33% SMS symptoms, 0%
Group II (*n* = 21)	Normal, 100%	Normal, 58% Increased SpEM, 21% Spontaneous Ny,21% SMS symptoms, 33%	Normal, 79% Increased SpEM, 21% SMS symptoms, 0%	Normal, 100% SMS symptoms, 0%

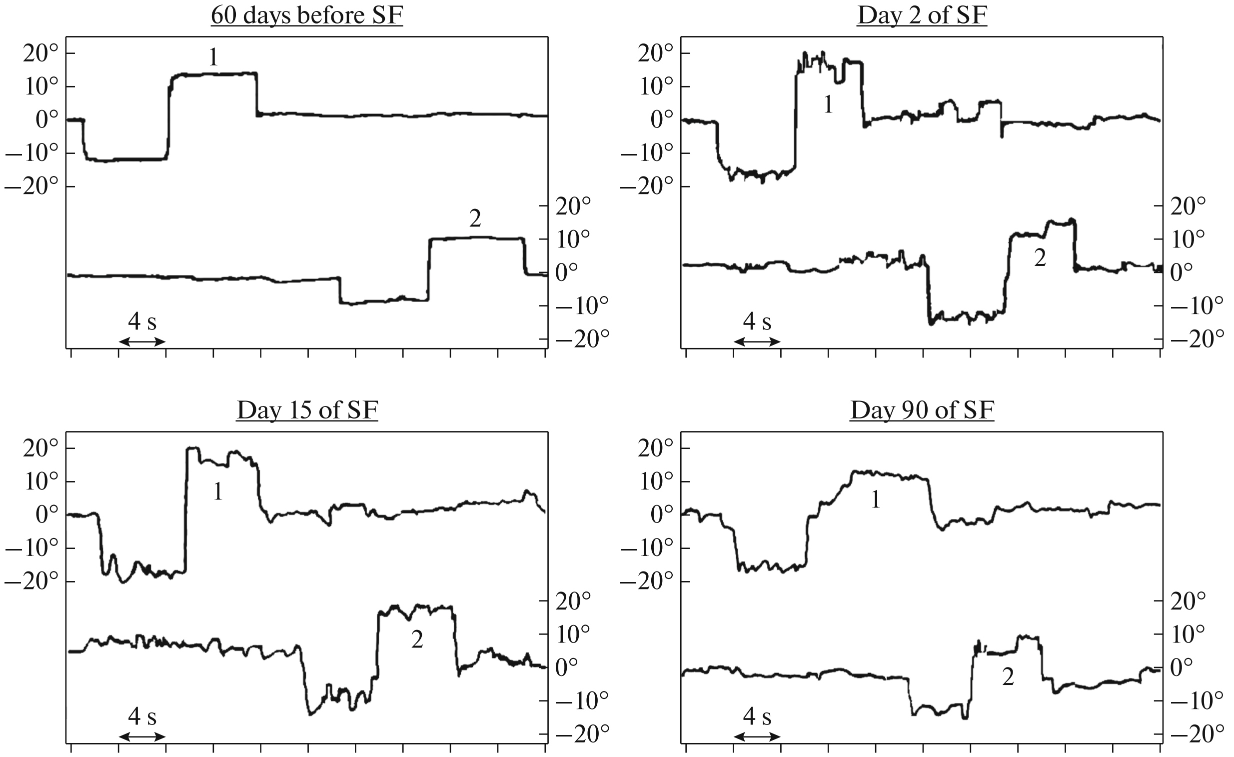
Static torsion otolith–cervical–ocular reflex (OCOR). All cosmonauts before SF displayed OCOR within the physiological norm.

The dynamics of gain of OCOR (gOCOR) during SF is detailed in Table 3.

Atypical OCOR responses (the absence or inversion of the otolith-ocular reflex) on day 2 of weightlessness were recorded in 55% of the subjects; on days 5–15, in 44%; on day 30, in 11%; on day 60, in 22%; on day 90, in 40%; and on day 120 an atypical otolith reflex was absent in all subjects but its statistically significant decrease was observed. The pattern and dynamics of the changes in OCOR were similar for both groups (the first SF and repeated SFs).

The OCOR asymmetry in the head tilts to the right or left shoulder on days 15, 30, and 60 of SF reached 30% and was almost absent on the remaining days of examination.

The dynamics of changes in gOCOR before, during, and after SF is shown in Fig. 2. As is evident,


60 days before SF

Day 2 of SF

Day 15 of SF

Day 90 of SF

Fig. 1. Fragments of SpEM native curves before and after space flight, SF (the ordinate shows the amplitude of eye movements, °, and the abscissa, time, s): (1) horizontal and (2) vertical eye movements.

gOCOR throughout SF decreased significantly but restored to its background level by day 8 after SF.

The native curves illustrating the development of atypical OCOR variants (the absence or inversion of the torsional ocular counter-rolling during the head tilt to the shoulder) during and after SF are shown in Fig. 3.

The native curves in Fig. 3 convincingly demonstrate that a head tilt to the shoulder before SF causes the torsional ocular counter-rolling in the range of 4–6°. In SF (days 5 and 90) and after SF (day 1), the torsional ocular counter-rolling in response to head tilt to the shoulder is either absent (the eye returns to initial zero position, which means the absence of OCOR) or changes its direction to that of the head tilt (OCOR inversion).

Note that, although no between-group differences were detectable among the participants of the Virtual experiment (stage 1), the analysis of the groups after SF, namely, the subjects after their first SF (group I, 26 cosmonauts) and after repeated SFs (group II, 21 cosmonauts) demonstrated statistically significant differences in the OCOR and SpEM characteristics and their dependence on the previous SF experience.

In group I, 33% of the subjects displayed no OCOR on days 1–2 after SF; 22%, OCOR inversion; and the remaining 45%, a statistically significant decrease (2- to 2.5-fold) in the amplitude of ocular counter-rolling. In addition, 69% of the subjects of this group complained of SMS symptoms on days 1–2 of the post-SF examination.

On days 4–5 after SF, normal OCOR was recorded in 45% of the group I subjects and a decreased reflex, in 55%. On days 8–9 after SF, normal OCOR was recorded in 72% of the subjects, while 28% displayed a decreased reflex to days 13–14 after SF. Statistical analysis demonstrated a significant decrease in gOCOR in group I on days 1–2 and 4–5 after SF as compared with the background and the data for days 8–9.

In group II, 29% of the subjects on days 1–2 after SF displayed normal OCOR; 64%, a statistically significant decrease in OCOR; and 7%, absence of OCOR. In addition, 33% of the subjects in this group had SMS symptoms during the first days of post-SF examination.

On days 4–5 after SF, normal OCOR was observed in 79% of the group II subjects and a decreased reflex in 21%; on days 8–9 after SF, all group II subjects had a normal OCOR.

Thus, an atypical OCOR (inversion or absence of the torsional ocular counter-rolling) after SF was mainly characteristic of the group I cosmonauts, who had no previous SF experience.

A comparative analysis of the coefficient of variation for gOCOR in groups I and II demonstrated that

Table 3. Dynamics of gain of OCOR (gOCOR) in space flight

Cosmonaut	Days of testing (*L,* baseline and *F,* days of flight)								
	L-60–30	*F*-2	*F*-5	*F*-15	*F*-30	*F*-60	*F*-90	*F*-120	*F*-150
First SF ($n = 4$)									
C1	0.21-r 0.22-l	Inv Inv	0.02-r 0.03-l	0.03-r 0.05-l	0.04-r 0.02-l	0.04-r 0.03-l	– –	0.04-r 0.04-l	0.06-r 0.05-l
C2	0.23-r 0.23-l	0.01-r 0.02-l	– –	– –	0.05-r 0.06-l	0.06-r 0.05-l	0.05-r 0.04-l	0.03-r 0.05-l	0.08-r 0.06-l
C3	0.21-r 0.20-l	– –	Inv Inv	0.06-r 0.03-l	– –	0.04-r 0.05-l	0.06-r 0.06-l	0.06-r 0.07-l	0.07-r 0.05-l
C4	0.22-r 0.22-l	0.03-r 0.01-l	0.05-r 0.06-l	0.02-r 0.03-l	0.04-r 0.03-l	Inv Inv	0.02-r 0.03-l	0.06-r 0.06-l	0.04-r 0.04-l
Repeated SF ($n = 5$)									
C5	0.21-r 0.21-l	Inv Inv	Inv –	0.04-r 0.06-l	0.05-r 0.05-l	0.03-r 0.04-l	0.04-r 0.06-l	– –	0.05-r 0.05-l
C6	0.19-r 0.20-l	– –	0.03-r 0.02-l	– –	0.07-r 0.05-l	0.06-r 0.06-l	– –	0.04-r 0.05-l	0.07-r 0.07-l
C7	0.24-r 0.22-l	– Inv	Inv Inv	Inv Inv	0.05-r 0.05-l	0.06-r 0.08-l	Inv –	0.06-r 0.06-l	0.04-r 0.06-l
C8	0.21-r 0.23-l	0.02-r 0.01-l	0.03-r 0.03-l	0.07-r 0.07-l	0.04-r 0.06-l	– –	0.05-r 0.03-l	0.05-r 0.02-l	0.07-r 0.05-l
C9	0.21-r 0.23-l	0.01-r 0.03-l	0.05-r 0.05-l	– –	0.06-r 0.06-l	0.07-r 0.07-l	– –	Inv Inv	0.08-r 0.07-l

(–) No OCOR; Inv, OCOR inversion; 0.19-r and 0.20-l are the gOCOR values of 0.19 and 0.20 for the head tilt to the right and left shoulders, respectively.

the gOCOR variance in group II was 1.5- to 2-fold smaller as compared with group I. A statistically significant increase in the coefficient of variation for gOCOR after SFs was observed in both groups to days 8–9 after SF.

The between-group comparison of gOCOR (Mann–Whitney test) demonstrates statistical significance of the difference in OCORaf between groups I and II to days 8–9 after SF.

Dynamic horizontal vestibular–cervical–ocular reflex (VCOR) and vestibular reactivity (VR). The gain of VCOR (gVCOR) before SF fell within the physiological norm (0.4–0.5) in all cosmonauts who participated in the Virtual experiment (stage 1).

After SF, the cosmonauts of group I were divided into two subgroups according to the gVCOR pattern. In subgroup 1 (10 subjects), gVCOR was increased to 0.7–0.8 starting from days 1–2 after SF and all cosmonauts complained of SMS symptoms on day 1. In subgroup 2 (16 subjects), gVCOR was drastically decreased to 0.1–0.15 or was almost zero as was demonstrated by the absence of compensatory horizontal ocular counter-rolling response. Only the cosmonauts (30%) who displayed both the vestibular rotatory nystagmus and compensatory ocular counter-rolling (increase in VR) complained of the SMS symptoms. Statistically significant changes in gVCOR in both subgroups of group I were observable to days 8–9 after SF.

A normal gVCOR was observed in 14 cosmonauts (~70%) of group II starting from days 1–2 after SF; five subjects of this group had an increased gVCOR and two subjects, a decreased gain. In this group, 33% complained of SAS symptoms; they displayed an increase in VR (pronounced nystagmus on the background of compensatory ocular counter-rolling).

Analysis of the coefficient of variation of gVCOR demonstrated that both groups displayed a statistically significant increase in the gVCOR variation to days 8–9 after SF. Note that the most pronounced increase in the coefficient of variation after SF was observed in the group I subjects with a decreased gVCOR.

The dynamics of post-SF changes in gVCOR and vestibular-induced nystagmus superimposing the compensatory ocular counter-rolling response to the head rotation around the longitudinal body axis are shown in Table 4.

In group I, 69% of the subjects on days 1–2 after SF displayed an increase in the vestibular nystagmus in response to head rotation; 50%, on days 4–5; and

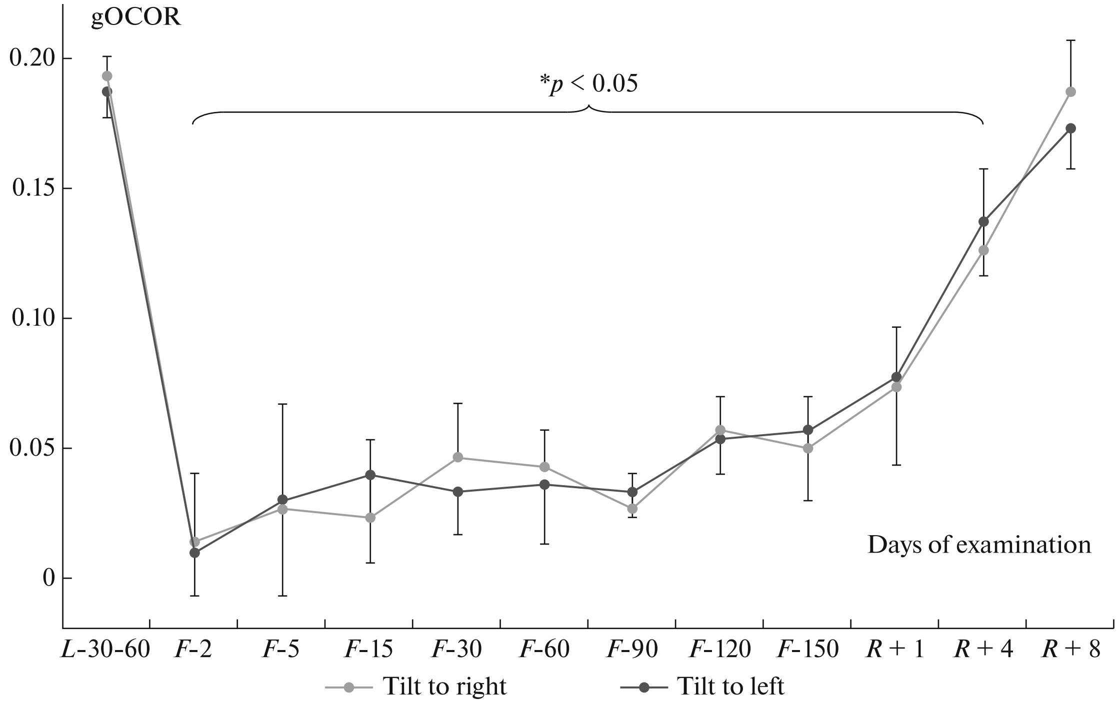


Fig. 2. Gain of the otolith-cervical-ocular reflex (gOCOR) before, during, and after SF. The ordinate shows gOCOR (ratio of the amplitude of torsional ocular counter-rolling to head tilt angle) and the abscissa, days of examination (*L,* baseline *F,* days in flight; and *R,* days after flight).

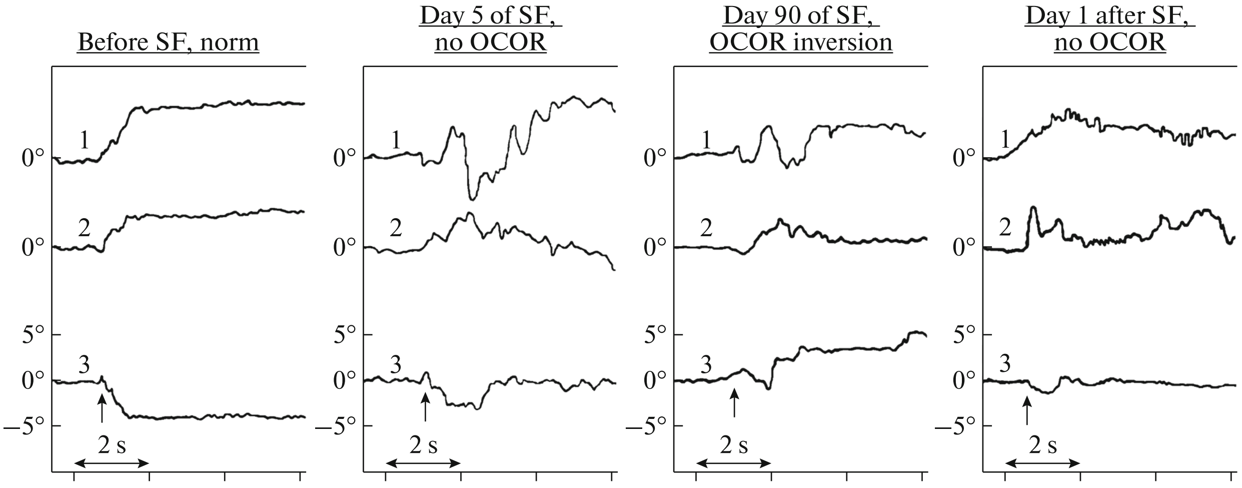


Fig. 3. Fragments of OCOR native curves before, during, and after space flight, SF (the ordinate shows the amplitude of eye movements, °, and the abscissa, time, s): (1) horizontal, (2) vertical, and (3) torsion eye movements. Arrow shows the beginning of head tilt to the shoulder.

12%, on days 8–9. Nystagmus was recorded both in the presence of a normal VCOR and on the background of a drastic decrease in the amplitude of compensatory ocular counter-rolling (Fig. 4).

The fragments of native curves recorded during head rotation around the body longitudinal axis (Fig. 4) before SF demonstrate an almost complete absence of the vestibular nystagmus on the background of compensatory horizontal ocular counter-rolling. On day 1 after SF did the group I subjects display a pronounced nystagmus both on the background of compensatory ocular counter-rolling and in its

Table 4. Dynamics of post-flight changes in gain of VCOR and VR

Characteristics of dynamic vestibular-ocular responses	Days of testing (L, baseline and R, days after flight)			
	L-60–30	R+1–2	R+4–5	R+8–9
	$M \pm \sigma$	$M \pm \sigma$	$M \pm \sigma$	$M \pm \sigma$
First SF ($n = 26$)				
Increase in gVCOR (10 cosmonauts)	0.45 ± 0.06	0.71 ± 0.12* ↑	0.78 ± 0.15*↑	0.55 ± 0.16
Decrease in gVCOR (16 cosmonauts)		0.10 ± 0.04* ↓	0.31 ± 0.11* ↓	0,42 ± 0.09
Vestibular nystagmus, T_{Ny}, %	–	47.3 ± 10.1* ↑ (18 cosmonauts)	32.9 ± 12.2* (13 cosmonauts)	25.6 ± 14.3 (3 cosmonauts)
Vestibular nystagmus, F_{Ny}, Hz		3.2 ± 0.6* ↑ (18 cosmonauts)	2.9 ± 0.7* (13 cosmonauts, 50%)	3.0 ± 0.9 (3 cosmonauts, 12%)
Vestibular nystagmus, A_{Ny}, °		11.1 ± 3.4* ↑ (18 cosmonauts)	9.4 ± 2.8* (13 cosmonauts)	8.7 ± 4.1 (3 cosmonauts)
Vestibular nystagmus, V_{Ny}, °/s		15.6 ± 7.0* ↑ (18 cosmonauts)	12.4 ± 8.3* (13 cosmonauts)	13.6 ± 6.0 (3 cosmonauts)
Repeated SF ($n = 21$)				
Increase in gVCOR (5 cosmonauts)	0.44 ± 0.07	0.62 ± 0.11	0.59 ± 0.11	0.51 ± 0.08
Normal gVCOR (14 cosmonauts)		0.53 ± 0.11	0.50 ± 0.15	0.46 ± 0.10
Decrease in gVCOR (2 cosmonauts)		0.22 ± 0.06	0.39 ± 0.11	0.43 ± 0.12
Vestibular nystagmus, T_{Ny}, %	–	28.3 ± 7.6* ↑ (7 cosmonauts)	19.1 ± 5.4* (4 cosmonauts)	–
Vestibular nystagmus, F_{Ny}, Hz		2.8 ± 0.5* ↑ (7 cosmonauts)	3.1 ± 0.8* (4 cosmonauts)	
Vestibular nystagmus, A_{Ny}, °		10.0 ± 4.1* ↑ (7 cosmonauts)	11.9 ± 3.7* (4 cosmonauts)	
Vestibular nystagmus, V_{Ny}, °/s		11.7 ± 5.6 ↑ (7 cosmonauts)	13.1 ± 6.2* (4 cosmonauts)	

* and ↑ denote statistically significant changes as compared with the baseline or, respectively, the pervious testing ($p < 0.05$); T_{Ny}, F_{Ny}, A_{Ny}, and V_{Ny} are characteristics of vestibular nystagmus (see Methods).

absence. As for the group II subjects, the nystagmic responses to head rotation were less pronounced in a statistically significant manner.

An increase in VR was observed in cosmonauts to days 8–9 after SF. In group I, 69% of the subjects who displayed an increase in nystagmus on the background of compensatory ocular counter-rolling complained of SAS symptoms on days 1–2 after SF.

In group II, an increase in VR and distinct nystagmus were observed in 33% of the subjects on days 1–2 after SF and in 19% on days 4–5. The VR of remaining cosmonauts matched the background during the entire post-SF period.

The duration of nystagmus (T_{Ny}) after SF in group I was 1.5- to 2-fold longer as compared with group II.

Correlation analysis of the vestibular function characteristics and SAS/SMS symptoms in weightlessness and after space flight. Correlation analysis of the results of the Virtual space experiment (stage 1) demonstrated a strong correlation between SpEM, OCOR, and SMS characteristics in 63% of the cosmonauts in the beginning (SF days 2–5) of adaptation to weightlessness and between SpEM and OCOR char-

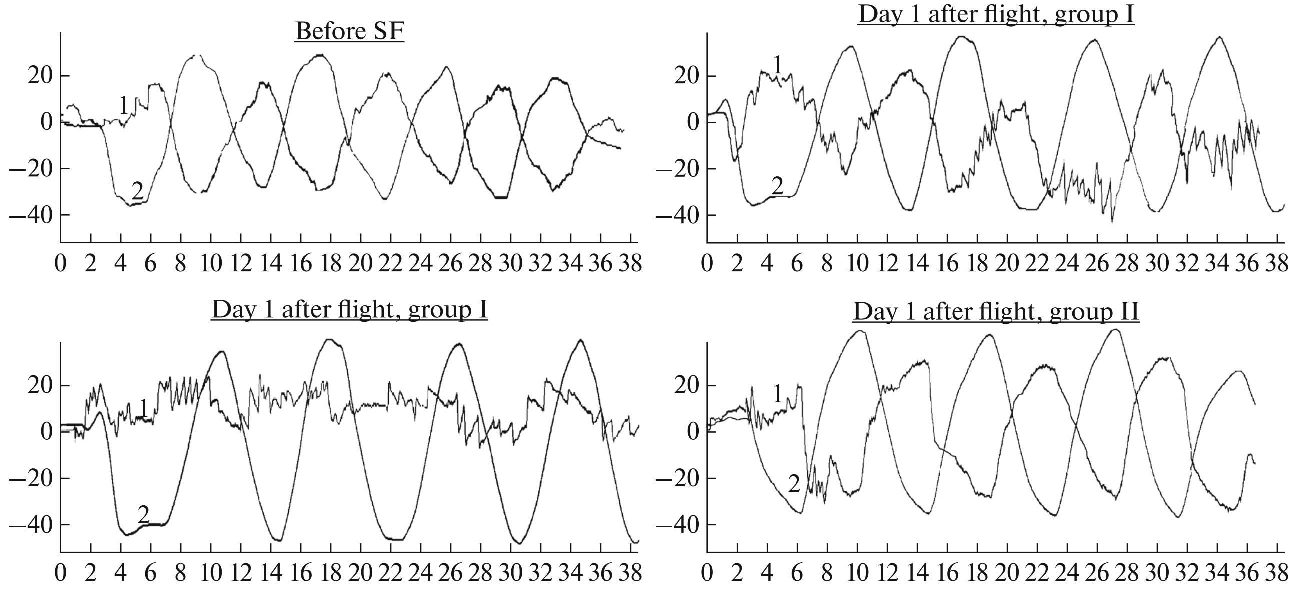


Fig. 4. Fragments of native curves for the head rotation around the longitudinal body axis before and on day 1 of space flight (SF) in the cosmonauts in their first SF (group I) and repeated SF (group II). The ordinate shows the amplitude of head and eye movements (°) and the abscissa, time (s): (1) eye movements (electro-oculography) and (2) head movements.

acteristics during the entire weightlessness period (r varying from about –0.55 to –0.93, $p < 0.05$).

A strong correlation between SpEM, OCOR, and SMS observed in the cosmonauts in weightlessness on days 2–5 of SF suggests deep and tight interactions between the central and peripheral parts of the vestibular system as well as the association between the vestibular and vegetative systems.

After SF (days 1–2), the group I subjects also displayed a strong correlation between SpEM, OCOR, and SMS. However, characteristic of this group was a negative correlation between the OCOR and VCOR/VR parameters starting from days 1–2 after SF ($r = –0.81$, $p < 0.05$) to days 4–5 ($r = –0.62$, $p < 0.05$).

The subjects of group II (with previous SF experience) displayed statistically significant changes in the state of VF and a weak negative correlation between OCOR and VCOR/VR characteristics only on days 1–2 after SF ($r = –0.38$).

DISCUSSION

The studies of the VF involving 47 cosmonauts after SF (nine were additionally examined during SF on board of ISS) have revealed typical responses of the vestibular system both during SF and after landing.

An increase in SpEM (appearance of spontaneous nystagmus in typical and atypical forms, as square-wave jerks) observed during and after SF is associated with the central mechanisms of the vestibular system and reflects the changes in the function of the vestibular nuclei, midbrain reticular formation, and cerebellar flocculus [13–16].

Under conditions of SF, the cosmonaut's otolith apparatus responds to the change in gravito-inertial environment, i.e., weightlessness. Either a drastic decrease in the amplitude (even to zero) of the compensatory torsional ocular counter-rolling during a static change in the head position or its inversion was characteristic of the recorded changes in OCOR during and after SF. Presumably, these changes are determined by both the reflex (weakening of the otolith afferent activity and retention of the cervical proprioceptive input) and central mechanisms (changes in the vestibular structures and the central structures interacting with them).

It is known that the interaction between two afferent flows, vestibular and cervical proprioceptive ones, underlies the OCOR. The passive cervical–ocular reflex is always accompanied by anticompensatory eye movements unlike the compensatory ocular counter-rolling of the vestibular–ocular reflex [17, 18]. The OCOR inversions observed during and after SF are most likely determined by the retention of cervical afferentation.

The results obtained in the experiments with primates, namely, those demonstrating that suppression or the absence of otolith-ocular reflex (OOR) as well as the changes in the excitability of the central vestibular structures demonstrated by a direct recording of the neuronal activity of the vestibular nerve and nuclei [16, 19] is the source of VF disorder, confirm that the peripheral part of the vestibular system and the central mechanisms are involved in the mechanism of atypical spontaneous and otolith-ocular responses under weightlessness conditions.

The absence of OCOR or its inversion in weightlessness and after long-term SFs, earlier demonstrated in the Russian space experiments [9, 20], were unobservable in the four astronauts who participated in the Neurolab (STS-90) mission [10]. The absence of OOR changes in these astronauts is most likely associated with that the VF was tested in a centrifuge both onboard and after SF. However, testing the OOR of 26 cosmonauts using a centrifuge only during the post-SF examination demonstrated a statistically significant decrease in the OOR amplitude [21].

The changes in SpEM and OCOR characteristics recorded in the Virtual space experiment during the initial adaptation to weightlessness (days 2–15) were periodically recorded during the entire SF; i.e., the adaptation (compensation) period was followed by disadaptation (decompensation) period. This alternation of compensation and decompensation periods during a long-term weightlessness has been earlier recorded by Russian researchers [2, 3]. The alternation of compensation and decompensation periods in the cosmonauts during SF was individual. No between-group differences in the VF characteristics were observed for the cosmonauts during their first or repeated experience of weightlessness. Comparison of the data on OCOR with the data on SpEM during SF revealed a strong correlation between these characteristics, which was independent of the presence or absence of the previous SF experience.

The alternation of compensation and decompensation periods during a long-term SF is another confirmation for the involvement of the central vestibular structures (vestibular nuclei, nuclei of the reticular formation, midbrain tegmentum nuclei, and vestibular cerebellar nuclei), which function in weightlessness at a different level as compared with the terrestrial conditions. There are no doubts that the cerebellum is involved in the adaptation (compensation) and disadaptation (decompensation) processes, since numerous pseudo-clinical cerebellar syndromes (square-wave jerks) were recorded when studying SpEM [22]. The results of model experiments (horizontal "dry" immersion) [23] also confirm the involvement of central mechanisms in development of atypical spontaneous and otolith–ocular responses.

Comparison of the results of VF examination of the cosmonauts for the first time in SF with the corresponding data for the cosmonauts after repeated SFs during the readaptation to terrestrial gravitation [24] demonstrated that (1) the repeated experience of a long-term SF shortened the period of VF adaptation in a statistically significant manner; (2) atypical VF disturbances (inversion or the absence of OCOR and the absence of VCOR) were characteristic of the subjects without any previous experience of long-term SFs; and (3) a drastic decrease in the level of tonic (static) vestibular excitability accompanied by an increase in the dynamic reactivity of the vestibular system was characteristic of the subjects without any previous long-term weightlessness experience.

The cosmonauts with previous experience of weightlessness (group II) displayed statistically significant changes in the VF state only on days 1–2 after flight and almost no atypical vestibular responses.

Thus, the post-SF data demonstrate that the adaptation to weightlessness is accompanied by central deep and long-term OCOR suppression, which requires a certain period to restore upon landing when the otolith function readapts to gravitation conditions.

The phenomenon of a decrease in static torsional ocular counter-rolling or its disappearance, observed in weightlessness and after SF, agrees with the histological data for the rats exposed to weightlessness. Histological examination demonstrated morphological signs of the hypofunction of utricle receptor cells, a decrease in the afferent input to vestibular nuclei, and signs of vestibular inflow to the cerebellar flocculus [25–28]. Morphological examination of multipolar neurons in the reticular formation [29–31] demonstrated a disturbance of the evolutionarily formed intersensory circuits in the central nervous system and formation of new circuits more adequate for spatial orientation in weightlessness.

The changes in gVCOR after SF suggests disturbance in the coordinated eye and head movements. This gain grew in some individuals and decreased down to zero in others. However, Cohen et al. [15, 16] observed suppression of gVCOR by 15–50% in primates during SFs; this decrease was retained to day 11 after SF. A decrease in gVCOR can be associated with either a decrease in or the absence of compensatory ocular counter-rolling, determined by disturbed otolith-canal interactions (associated with the central deafferentation of otolith signal) or inhibition (rejection) of the vestibular nuclei that lost their adequacy via the cerebellar control mechanism [22].

A drastic increase in the intensity of vestibular nystagmus in response to horizontal head rotation, observed in many cosmonauts after SF, suggests an increase in the dynamic excitability of the vestibular input. An increase in the dynamic component in weightlessness was earlier observed in the experiments with frog vestibular receptors [32]. Gualtierotti [32] succeeded in recording an increase in the dynamic neuronal excitability in the vestibular nerve during the first 12 h of SF and in revealing the trend of transformation of the initially tonic activity type of these neurons into a phasic type. Thus, it was for the first time demonstrated that some static receptor cells in weightlessness could function as dynamic ones [32].

The otoliths after SF and landing are again subject to the gravity and the response of the semicircular canals supposedly should be weakened in the case of a reciprocal pattern of the otolith-canal interaction [33, 34]. Nonetheless, this is unobservable, which can be explained by the central deafferentation of the otolith signal, which appeared during SF and retained in the initial readaptation period.

The observed negative correlation between OCOR and vestibular reactivity (VCOR/VR) characteristics suggests reciprocal relationships between the otoliths and semicircular canals in the examined group of cosmonauts after SF; in other words, an increase in the dynamic reactivity of the vestibular system is observed on the background of a decrease in the level of static vestibular excitability.

However, weightlessness can influence the otolith function and the function of semicircular canals both directly because of the loss of gravitational impact and in an indirect manner because of removal of the support afferentation and a decrease in proprioceptive afferentation via the central integrative multisensory structures in the central nervous system, involved in convergence of afferent signals of different sensory modalities (first and foremost, visual, vestibular, supporting, and locomotor). The experiments with simulated weightlessness ("dry" horizontal immersion) demonstrated appearance of spontaneous nystagmus during the first days after immersion as well as the absence or inversion of OCOR [23].

The observed identical VF disturbances during the first days of adaptation to weightlessness (days 2–5 of SF) and readaptation to terrestrial conditions (days 1–4 after SF) were accompanied by complaints of SAS and SMS symptoms of various intensities. However, the onboard examinations during SF and completion of readaptation recorded no complaints of SAS and SMS symptoms although the changes in VF characteristics were recorded.

Thus, dizziness, spatial illusions, orientation disturbances, and atypical spontaneous and vestibular-ocular responses observed in the initial SF period as well as on days 0 and 1 after landing were not characteristic of certain individuals but rather the regular responses of body sensor systems under conditions of altered gravity. This confirms the development of SAS, which transformed to SMS on reaching a clinical level [35, 36].

CONCLUSIONS

The studies in the framework of the Virtual space experiment (stage 1) demonstrate that weightlessness causes the following phenomena also observable during the post-SF readaptation:

1. A decrease in or complete elimination of the tonic (static) component in the vestibular-ocular responses (the absence or inversion of torsional ocular counter-rolling) because of central deafferentation, "rejection" of the vestibular signal from the systems controlling eye movements changed in weightlessness during adaptation and initial readaptation.

2. An increase in the dynamic reactivity of the semicircular canals of the vestibular system (a decrease in the threshold and an increase in the intensity of the nystagmus during head rotation) on the background of decreased tonic component;

3. Significant changes in the VF in weightlessness, which were independent of the previous SF experience;

4. Regular patterns of the VF character and dynamics, namely, alternation of adaptation and disadaptation periods in weightlessness; and

5. Significant changes in the VF after landing, which depended on the pervious SF experience, namely, the subjects without previous weightlessness experience had longer readaptation period and more pronounced VF disorders.

The VF disorders observed during the first days of SF and after SF were very similar and the recorded parameters displayed pronounced correlation, suggesting that these disorders can be regarded as SAS and SMS manifestations.

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REFERENCES

1. Kornilova, L., Grigorova, V., and Bodo, G., Vestibular function and sensory interaction in space flight, *J. Vestibular Res.*, vol. 3, no. 3, p. 219.
2. Kornilova, L.N., Grigorova, V., Mueller, Ch., et al., The vestibular system. Intersensory interaction. Space perception and spatial orientation. Space adaptation syndrome and space motion sickness, in *Orbital'naya stantsiya "MIR": Kosmicheskaya biologiya i meditsina* (Orbital Station Mir: Space Biology and Medicine), Moscow, 2002, vol. 2, p. 208.
3. Kornilova, L.N., Naumov, I.A., and Kozlovskaya, I.B., Neurosensory studies of the vestibular function in humans, in *Kosmicheskaya meditsina i biologiya* (Space Medicine and Biology), Grigor'ev, A.I. and Ushakov, I.B., Eds., Voronezh: Nauchn. Kn., 2013, p. 278.
4. Young, L.R. and Sinha, P., Spaceflight influences on ocular counterrolling and other neurovestibular reactions, *Otolaryngol. Head- Neck Surg.*, 1998, vol. 118, p. 31.
5. Baumgarten von, R., Weitzig, J., and Vogel, H., Static and dynamic mechanisms of space vestibular malaise, *Physiologist*, 1982, vol. 25, no. 6, p. 33.
6. Watt, D.G., The vestibulo-ocular reflex and its possible roles in space motion sickness, *Aviat., Space Environ. Med.*, 1987, vol. 58, no. 2, p. 170.

7. Clement, G. and Berthoz, A., Vestibulo-ocular reflex and optokinetic nystagmus in microgravity, *Adv. Otorhinolaryngol.*, 1988, vol. 42, p. 1.
8. Thornton, W.E., Uri, J.J., Moore, T., and Pool, S., Studies of the horizontal vestibulo-ocular reflex in spaceflight, *Arch. Otolaryngol., Head Neck Surg.*, 1989, vol. 115, no. 8, p. 943.
9. Clarke, A. and Kornilova, L., Ocular torsion response to active head-roll movement under one-g and zero-g conditions, *J. Vestibular Res.*, 2007, vol. 17, nos. 2–3, p. 99.
10. Moore, S., Clement, G., Raphan, T., and Cohen, B., Ocular counterrolling induced by centrifugation during orbital space flight, *Exp. Brain Res.*, 2001, vol. 137, nos. 3–4, p. 323.
11. Reschke, M., Bloomberg, J., and Paloski, W., Sensorimotor recovery following spaceflight may be due to frequent square-wave saccadic intrusions, *Aviat., Space Environ. Med.*, 2004, vol. 75, no. 8, p. 700.
12. Clarke, A., Teiwes, W., and Scherer, H., Evaluation of the torsional VOR in weightlessness, *J. Vestibular Res.*, 1993, vol. 3, no. 3, p. 207.
13. Kozlovskaya, I.B., Ilyin, E.A., Sirota, M.G., et al., Studies of space adaptation syndrome in experiments on primates performed on board of soviet biosatellites "Cosmos-1887", *Physiologist*, 1989, vol. 32, no. 1, p. 45.
14. Sirota, M.G., Babaev, B.M., Belozerova, I.N., et al., Bioelectric activity of vestibular nuclei under microgravity conditions, in *Rezul'taty issledovanii na biosputnikakh* (The Results of Studies on Biosatellites), Gazenko, O.G, Ed., Moscow: Nauka, 1992, p. 29.
15. Cohen, B., Tomko, D., and Guedry, F., Vestibular and sensorimotor function in microgravity, *Ann. N. Y. Acad. Sci.*, 1992, vol. 682, p. 340.
16. Cohen, B., Yakushin, S., Holstein, G., et al., Vestibular experiments in space, *Adv. Space Biol. Med.*, 2005, vol. 10, p. 105.
17. Usachev, V.I., Interaction between vestibular, optical, and proprioceptive sensory systems during the process of rotatory nystagmus, *Sens. Sist.*, 1995, vol. 9, no. 4, p. 42.
18. Ischebeck, B.K., de Vries, J., van Wingerden, J.P., et al., The influence of cervical movement on eye stabilization reflexes: A randomized trial, *Exp. Brain Res.*, 2017, no. EXBR-D-17-00055.
19. Correia, M., Perachio, A., and Dickman, J., Vestibular primary afferent and vestibulo-ocular changes in rhesus monkey following 14 days of microgravity, *Soc. Neurosci. Abstr.*, 1990, vol. 16, p. 735.
20. Kornilova, L., Naumov, I., Azarov, K., and Sagalovich, V., Gaze control and vestibular-cervical- ocular responses after prolonged exposure to microgravity, *Aviat., Space Environ. Med.*, 2012, vol. 83, no. 12, p. 1123.
21. Hallgren, E., Kornilova, L., Fransen, E., et al., Decreased otolith-mediated vestibular response in 25 astronauts induced by long duration spaceflight, *J. Neurophysiol.*, 2016, vol. 115, no. 5, p. 3045. doi 10.1152/jn.00065.2016.
22. Cohen, B., John, P., Yakushin, S., Buettner-Ennever, J., and Raphan, T., The nodulus and uvula: Source of cerebellar control of spatial orientation of the angular vestibulo-ocular reflex, *Ann. N. Y. Acad. Sci.*, 2002, vol. 978, p. 28.
23. Kornilova, L., Naumov, I., and Makarova, S., Static torsional otolith-cervical-ocular reflex after prolonged exposure to weightlessness and a 7-day immersion, *Acta Astronaut.*, 2011, vol. 68, nos. 9–10, p. 1462.
24. Naumov, I.A., Kornilova, L.N., Glukhikh, D.O., et al., Vestibular function after repeated space flights, *Aviakosm. Ekol. Med.*, 2015, vol. 49, no. 6, p. 33.
25. Krasnov, I.B., Untriculus and nodulus of rats exposed to microgravity, *Trudy Mezhdunarodnogo simpoziuma po biosputniku "Kosmos"* (Proc. Int. Symposium on "Kosmos" Biosatellite), Leningrad, 1991, p. 59.
26. Krasnov, I.B. and Dyachkova, L.N., The effect of space flight on the ultrastructure of the rat cerebellar and hemisphere cortex, *Physiologist*, 1990, vol. 33, p. 29.
27. Krasnov, I.B., Electron microscopy analysis of the structural elements of the vestibular input to nodulus Purkinje's cells in rats exposed to a 9-day space flight, *Aviakosm. Ekol. Med.*, 2008, vol. 42, no. 4, p. 20.
28. Krasnov, I.B., Purkinje's cells in the vestibular and proprioceptive segments of rat's cerebellum following 14-day space flight, *Aviakosm. Ekol. Med.*, 2009, vol. 43, no. 4, p. 43.
29. Belichenko, P. and Leontovich, T., Changes in the giant multipolar neurons of rat reticular formation and brain stem after 14-day spaceflight, *Aviakosm. Ekol. Med.*, 1992, vol. 26, nos. 5–6, p. 24.
30. Belichenko, P., Machanov, M., Fedorov, A., Krasnov, I., and Leontovich, T., Effects of space flight on dendrites of the neurons of the rat's brain, *Physiologist*, 1990, vol. 33, p. 12.
31. Dyachkova, L., Ultrastructural characteristics of plastic changes in the brain cortex of rats exposed to space flight, *Physiologist*, 1991, vol. 34, p. 185.
32. Gualtierotti, T., Gravity only dependent receptor field of the vestibular sensors: Its significance in orbital flight, *Physiologist*, 1981, vol. 24, no. 6, p. 103.
33. Kurashvili, A.E. and Babiyak, V.I., Functional interaction of semicircular ducts and otolithic apparatus, in *Fiziologiya vestibulyarnogo analizatora* (Physiology of Vestibular Analyzer), Moscow: Nauka, 1998, p. 119.
34. Babiyak, V.I. and Yanov, Yu.I., *Vestibulyarnaya funktsional'naya sistema* (Vestibular System Function). St. Peterburg: Gippokrat, 2007.
35. Thornton, W., A rationale for space motion sickness, *Aviat., Space Environ. Med.*, 2011, vol. 82, no. 4, p. 467.
36. Thornton, W. and Bonato, F., Space motion sickness and motion sickness: Symptoms and etiology, *Aviat., Space Environ. Med.*, 2013, vol. 84, no. 7, p. 716.

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